A STUDY OF AETIOLOGY, EARLY RECOGNITION, INVESTIGATION AND INTERVENTION IN HYPERTENSIVE DISEASE OF PREGNANCY

Volume I of II

by

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PREFACE

When a patient embarks on pregnancy, she expects to remain in good health and, after the minimum of interference, to deliver unaided a healthy, well grown and vigorous child. Reproduction is a natural function, but experience has shown that, in many instances, a pregnant woman suffers from some abnormality of pregnancy or labour, increasing the risk for both her and her child. Hypertension in pregnancy is one such abnormality with well recognised risks for both mother and baby. The cause of the blood pressure rise is unknown but appears to be related to an inability of the mother to adapt to the normal changes of pregnancy, with a deficiency of plasma volume expansion and an increased peripheral resistance. The reason for the failure in the physiology of a given pregnancy may be genetic or hereditary in origin, an abnormal reaction to a given pregnancy or may have its primary source in some feature of the environment.

While the incidence and the presentation of any disease is easily studied, aetiological factors and the risks to mother or baby are more difficult to assess. With changes in the environment, improvement in antenatal care and improved general health, there has been a reduction in most major complications of pregnancy, including severe preeclampsia/eclampsia. As the incidence of the condition falls, the importance of the rarer atypical forms increases. This makes the study and management of the condition more problematical as the number of patients seen by an average obstetrician is greatly reduced. Despite the fall in the incidence of the severe condition, the overall incidence of all types of preeclampsia has not altered, remaining at around 25% in primigravid and 10% in multigravid patients. The maternal death rate associated with it has not changed for over 20 years. This has led to a call for specialised teams to be set-up to study and manage the condition.

One such team was formed at the beginning of 1981 in the Glasgow Royal Maternity Hospital under the direction of the author. The aim of the group was to study the aetiology, presentation, assessment of risk and morbidity and management of hypertensive disorders in pregnancy. There has been an attempt to develop methods of screening, of prevention and of treatment that could then be used in other centres. The basis of this thesis is the history of the formation and workings of this group.

The team consisted of obstetricians, midwives, haematologists and biochemists. All clinical and research work was conceived, instigated, directed and largely carried out by the author who saw and assessed all hypertensive patients attending the GRMH over the nine year period.

Much of the previous work carried out in hypertension in pregnancy has been done

retrospectively after the pregnancy is over and the outcome known. Retrospective analysis does not help the assessment of risk to a patient at the time of presentation of the problem during the pregnancy and does not help in the management of the case. The main objective of the work was to look at the problems of hypertension in a prospective way.

Although the concept, planning, direction and organisation of the studies were the author's, much of the laboratory and some of the ward work was carried out by other members of the team. A sincere debt is owed to many people.

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The author owes a substantial debt of gratitude to the following people.

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List of Abbreviations used in this Thesis.

Abbreviation	Meaning
AII	Angiotensin II
Alt	Alanine aminotransferase
Ast	Aspartate aminotransferase
BP	Blood Pressure
CSA	Common Services Agency, SHHD
DHSS	Department of Health and Social Services
ISSHP	International Society for the Study of Hypertension in Pregnancy
γ-GT	Gamma Glycerol Transferase
GRMH	Glasgow Royal Maternity Hospital
HELLP	Haemolysis, Elevated Liver enzymes, and Low Platelets
FDP's	Fibrin Degradation products
MPV	Mean Platelet Volume
PDW	Platelet Distribution Width
PET	Preeclampsia
PIH	Pregnancy Induced Hypertension
PGI/PGI_2	Prostacyclin
PGIM	Prostacyclin metabolites
(6-Keto-)$PGF_{1\alpha}$	Stable metabolite of Prostacyclin
PGE_2	Prostaglandin E_2
$PGF_{2\alpha}$	Prostaglandin $F_{2\alpha}$
RIA	Radioimmuno Assay
SHHD	Scottish Home and Health Department
TxA_2	Thromboxane A_2
TxB_2	The stable metabolite of TxA_2

DECLARATION

The studies presented in this thesis were performed in the University Department of Obstetrics and Gynaecology at Glasgow Royal Maternity Hospital, between January 1981 and December 1989. The Daycare Assessment Unit, the Hypertension Management Team and all protocols of investigation and management arose from the ideas of the author. The clinical studies were conceived, designed and largely performed by the author in person. The clinical studies on prostacyclin and thromboxane in pregnancy described in Chapter 9 of this thesis were conceived and designed by the author. They were performed in association with Dr. Ian A. Greer then of the University Department of Medicine in Glasgow Royal Infirmary. I was assisted in the collection of clinical material by Drs Myriam Bonduelle, Alan Cameron, Steingrimour Bjornsson, Fiona Fairlie and Alan Mathers, research fellows of the University Department of Obstetrics and Gynaecology. Sister Helen Cheyne has worked with me since 1985.

The radioimmunoassays used to measure prostacyclin and thromboxane metabolites were developed and performed by Dr Margaret McLaren, then of the University Department of Medicine and the studies of platelet size were carried out by Miss Carol Fraser of the Department of Haematology in Glasgow Royal Infirmary. The original concept, planning and organisation of the studies, much of the sampling, analysis of the data, interpretation of the results, computer assessment and the opinions expressed in this thesis are, however, solely those of the author.

Many of the studies in this thesis have already been published or presented in learned journals and meetings. A list of these papers published are as follows:-

Walker J J, Crooks A, Erwin L, Calder A A. Labetalol in pregnancy induced hypertension; fetal and maternal effects: In The investigation of Labetalol in the Management of Hypertension in Pregnancy. Eds Riley and Symonds E M. (1982) pp 148 - 160, Amsterdam: Excerpta Medica.

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Walker JJ. Antihypertensive therapy in pregnancy. (Accepted for publication in Clinics of North America).

Walker, J.J., Mathers, A.M., Bjornsson, S., Cameron, A.D., Fairlie, F. The effect of acute and chronic antihypertensive therapy on the maternal and fetal cardiovascular system. (Accepted for publication Eur. J Obstet Gynecol Rep Biol)

The Summary

After a critical review of the literature, it was decided to study the risks, presentation and management of patients with pregnancy hypertension in our population, the role of antihypertensive drug therapy on disease stabilisation and progression and the causes of the prostaglandin/thromboxane imbalance and the increased platelet consumption.

The incidence of eclampsia has fallen from the mid 1930's to the early 1980's. The largest reduction occurred at around 1950. There were 74 maternal deaths in the first decade, 14% of all eclamptics. There was only 1 maternal death in the last two decades, 5% of the eclamptics. Therefore, not only has the incidence of eclampsia fallen, but also the incidence of maternal death from eclampsia. Perinatal survival has improved over the five decades. However, from 1973 to 1982 one-third of the babies born of mothers with eclampsia died, demonstrating that a high risk remains. Delivery, with various methods of sedation, was the most common management. Only since 1973 have antihypertensive drugs have been used regularly.

Investigation of blood pressure variation showed that over 60% of patients had a blood pressure variation of more than 5 mmHg in both systolic and diastolic blood pressure when 2 measurements were taken 10 minutes apart. An average of 4 blood pressure readings taken between 30 and 60 minutes appeared to give an accurate estimate of a patient's blood pressure. Automated blood pressure monitoring showed similar variations, but the Dinamap automatic blood pressure recorder tended to measure the diastolic blood pressure about 8 mmHg lower than the nursing staff. A single blood pressure reading was not used for diagnosis or for making management decisions.

At Daycare, it was found that if the 3 parameters of blood pressure, uric acid and platelet count were all normal, 95% of the patients would remain normal throughout the rest of their pregnancy without the need for any specialised care. This constituted over 50% of the patients who attended daycare. If any of these parameters were abnormal, 40% of the patients would progress to a more severe form of the disease. Most the patients referred to day care attended only once, and then returned to the antenatal clinic for routine care. This has reduced the number of admissions and number of inpatient days spent because of hypertension.

Using multiple regression analysis of the various parameters, it was found that proteinuria was associated with earlier gestations, and growth retardation with later onset disease. Uric acid was associated negatively with platelet count and positively with abnormalities of liver enzymes and diastolic blood pressure, suggesting that it may be a marker of systemic involvement. The causes of the changes in albumin are multiple and not related only to proteinuria.

An increase of platelet size was only seen if severe hypertension developed after 34

weeks. This suggests that those developing severe preeclampsia later in pregnancy would appear to have a more chronic onset with a prolonged stimulus to platelet activation and increased platelet turnover.

Associated studies were carried out on prostacyclin levels. Studies in hypertensive patients showed that patients with severe disease all had unrecordable levels of prostacyclin (<5 ng/ml), and that about 50% of those with moderate disease also had unrecordable levels. Thromboxane did not appear to be elevated in most patients. Although the prostacyclin/thromboxane balance is disturbed, it is mostly due to deficiency of prostacyclin rather than an elevation of thromboxane.

A serial study of prostacyclin showed that levels fell below the lower limit of the assay before the onset of hypertension. This suggests that the ability to produce prostacyclin was exhausted prior to the development of the hypertension.

Studies of antihypertensive drugs in acute hypertension showed that hydrallazine, oral labetalol and oral nicardipine could adequately reduce the diastolic blood pressure over a period of 30 minutes to 1 hour. This reduction was maintained over the next 2 hours.

A randomised study of labetalol against bed rest in mild to moderate pregnancy hypertension showed that bed rest alone did not lower blood pressure or slow the progression of the disease, whereas labetalol therapy significantly reduced blood pressure and appeared to slow the progression of certain disease parameters. However, there was no difference in the outcome of the pregnancies between the two groups. If the diastolic blood pressure was below 100 mmHg, there did not appear to be any benefit from early therapy. There is no evidence that these medications are harmful to the mother or baby.

A further study of 186 primigravidae with severe proteinuric preeclampsia was carried out. Adequate reduction of blood pressure was achieved in 95% patients using either labetalol alone or in combination with a vasodilator drug. The average length of treatment was 15 days. There was no change in the fetal heart rate patterns or blood flow parameters as measured by Doppler velocimetry with commencement of therapy. Maternal monitoring, including uric acid, blood pressure, proteinuria and platelet count did not relate to fetal wellbeing. Gestation at presentation was the most significant parameter. After 30 weeks almost all the babies did well. In the group presenting before 30 weeks, outcome was associated with evidence of fetal compromise. If the results of fetal monitoring were satisfactory, the outcome was good irrespective of maternal disease severity.

Over the last 9 years 3,885 hypertensive patients have been reviewed. Prophylactic anticonvulsants were not used unless there were obvious signs of severe progressive hypertension with evidence of imminent eclampsia. The incidence of eclampsia in

these patients was low suggesting that there is no need for routine anticonvulsant therapy.

It is concluded that a stepwise approach to the management of hypertension in pregnancy is possible. Most patients can be managed as outpatients without the need for intervention. Patients who have blood pressure persistently greater than 100 mmHg can be treated safely with antihypertensive therapy as long as the baby is well. This is associated with a reduction of hospital admission, reduction of intervention and a general reduction in the perinatal mortality rate.

CHAPTER 1

INTRODUCTION TO THE THESIS

There is much confusion concerning the condition of hypertension and convulsions in pregnancy, although the association of convulsions and maternal death has been known since ancient times. The word "eclampsia" comes from the Greek verb "eclamptien" meaning "to flash out". This relates to its sudden onset or to the flashing hallucinations experienced in the prodromal phase. Hippocrates described the condition in "On The Sacred Disease". Unfortunately he did not distinguish eclampsia from epilepsy, but stated that "it proves fatal to women in the state of pregnancy" (Chesley, 1980). Over the centuries, it was noted that the presence of convulsions and coma were ominous signs in the presence of difficult labour and often resulted in the death of both mother and fetus (Chesley, 1980). In the sixteenth century, Gabelchoverus noted that pregnancy was a cause of epilepsy and described the epigastric pain associated with this. He felt that the pain was a sign that the cause of the convulsion came from the uterus (Chesley, 1980). Mauriceau (1668), refers to eclampsia as does Denman (1768) in a book dedicated to the problem along with puerperal fever. He recognised eclampsia as a major cause of morbidity and mortality.

Once it was realised that the condition was specific for pregnancy, it was thought by many to be a form of renal disease. In 1843 Lever found that patients with eclampsia had proteinuria (Lever, 1843). Although he realised that eclampsia was different from renal disease since the proteinuria disappeared after delivery, others thought that the condition was very similar to that seen in glomerulonephritis. Simpson, who found proteinuria at about the same time, saw contracted kidneys in one of his patients and felt that this was the cause of the problem (Simpson, 1843). This became the popular opinion for some time. It was not until the development of methods of assessment of renal function and finally the renal histology studies of Sheehan (1950) and McCartney (1964), that the timing of the stages of the disease was realised. Both Sheehan and McCartney stated that renal lesions were present only when the patient had proteinuria and since this was a late manifestation of the condition called preeclampsia, it could not be a primary cause of the condition.

It was not until the late nineteenth century that hypertension was first noted to be associated with eclampsia (Ballantyne, 1885; Cook and Briggs, 1903). In 1896, essential hypertension was first differentiated from renal hypertension. However, as it was originally called 'senile plethora', many obstetricians felt that none of their (mostly young) patients could have this condition (Chesley, 1980). It was not until the 1940's that the possibility of essential hypertension as a cause of hypertension in pregnancy was accepted. From this time it was realised that renal disease was a relatively rare cause of hypertension in pregnancy. Although pregnancy could occur in a patient with preexisting essential hypertension, renal disease or other

hypertensive disorder, there was a specific hypertensive syndrome arising in pregnancy that disappeared when the pregnancy was over and apparently carried no long term sequelae (Chesley, Annitto and Cosgrove, 1976).

The realisation that this pregnancy "associated" hypertension often antecedes convulsions, led to the term "preeclampsia". This term was initially used for the immediate prodromal stage of eclampsia but now is applied to patients with milder forms of the disease. Although eclampsia is associated with hypertension, it is not an obligatory endpoint of the condition. Convulsions are independent of the severity of the disease. 'Mild' preeclampsia may be associated with convulsions and 'severe' may not. Between 15 and 20% of the patients suffering from "eclampsia" had no record of hypertension prior to the seizure (Cruickshank, 1923; Cruickshank, Hewitt and Couper, 1927) Although these early findings could partly be due to inadequate records, the results have been confirmed by more recent workers (Sibai *et al.*, 1981b).

Modern thinking appears to simplify classification of hypertension in pregnancy. However, hypertension in pregnancy is not a single disorder, but has multivariant causes, dependent on different aetiologies and on the mother's varying response to the stimuli. It is often not possible to be sure to which group a patient belongs at the time of presentation. Postnatal followup may demonstrate, for example, renal pathology causative of the hypertension.

Over 100 names have been used in the past to define the different forms of hypertension in pregnancy and efforts have been made to simplify this (Rippman, 1968; Hughes, 1972; Nelson, 1955b) The modern term of "pregnancy induced hypertension" is no great improvement, as it implies aetiology.

Until the underlying aetiology is understood, however, the disease will continue to be described in the clinical way it presents or develops. The "Organisation Gestosis", or EPH-Gestosis, was the first international organisation formed for the study of this clinical condition. It uses the clinical signs of Edema, Proteinuria and Hypertension as the basis of the diagnosis. The presence of any two of these signs is all that is required for the diagnosis of 'gestosis' but the dominance of the oedema as the presenting sign is over-stressed and the hypertension is given little prominence (Rippman, 1968). The "International Society for the Study of Hypertension in Pregnancy" (ISSHP) is devoted to the study of all aspects of the pregnancy conditions associated with hypertension. The emphasis is on hypertension arising for the first time during pregnancy and its various manifestations (Davey and MacGillivray, 1988). These methods of classification lead to confusion, as some patients with "gestosis" do not have "preeclampsia". It is important to realise that these societies are describing different groups of patients, although there is a considerable degree of overlap.

The problems with the definitions of the condition make comparison of the apparent incidence and risks difficult. It would appear that hypertension in human pregnancy occurs in around 25% of primigravid and in 10% of the multigravid mothers, but the incidence varies with the experience of different authors (Chamberlain *et al.*, 1978b; Nelson, 1955b; MacGillivray, 1958; Common Services Agency., 1986). In Western society, despite improved environmental conditions, improved maternal health, greatly improved antenatal care and reduction in perinatal loss in association with hypertensive syndromes, the rate of maternal death attributed to pregnancy hypertension has not changed for twenty years (DHSS, 1969; DHSS, 1974; DHSS, 1979; Turnbull, 1987; Turnbull *et al.*, 1989; Scottish Home And Health Department, 1978; Scottish Home And Health Department, 1987; Scottish Home And Health Department, 1989). In 75%-81% of the maternal deaths, avoidable factors were found. Most of these were associated with failure to recognise warning signs. There was a failure to initiate proper therapy rather than the use of inadequate or wrong therapy. The reduction in the incidence of the severe forms of hypertensive disease in pregnancy in the United Kingdom has led to reduction in the exposure of obstetricians to the problem and a lowering of their ability to manage the severe cases as they arise. The modern clinician is caught in a clinical dilemma. Because the incidence of severe forms of the condition appears to be reducing, while the overall incidence of all forms of hypertension appears to be unchanged, the risk of the hypertension in pregnancy to the mother and baby would appear to be diminishing. Therefore, it is difficult to justify continued admission to hospital for all cases of hypertension in pregnancy, especially when the risks appear to be small and the patient feels so well. As the rate of maternal death has not changed and hypertension in pregnancy is still a significant contributor to the perinatal mortality rate (Common Services Agency., 1986; Scottish Home And Health Department, 1989), the more cautious approach of admission to hospital for observation might also seem reasonable. Since pregnancy has a finite length and the admission to hospital will be only for a short stay, the price to pay for admission is small and the rewards of success appear to be great. Every satisfactory outcome following admission to hospital for the management of this condition leads to a further positive reinforcement that it is the best approach (De Sweit, 1985). A logical approach to the management of pregnancy hypertension is difficult because of the emotional and deep seated feelings it can produce (De Sweit, 1985; Hodgson, 1985). Anything that is thought to put the mother or baby at risk is rejected in return for the tried and tested 'status quo'. However, there has been no randomised study carried out proving that admission to hospital is beneficial to mother or baby (Crowther and Chalmers, 1989). Since the situation is confused, and experience limited, there has

been a call for the setting up of specialised teams of clinicians to manage and study all patients who present with hypertension in pregnancy (Turnbull *et al.*, 1989).

In 1980, the author initiated a programme to study hypertension in pregnancy. This consisted of investigations into the incidence of hypertensive problems in the hospital practice, the maternal and fetal morbidity associated with the hypertension, specific aspects of aetiology, the role of screening tests for hypertensive risk, the role of early intervention therapy using hypotensive regimes in both mild to moderate and severe pregnancy hypertension and the development of standardised protocols to simplify patient management. It was hoped that the majority of the screening, monitoring and treatment could be achieved as an outpatient thus reducing the need for hospitalisation and allowing more intensive care to be provided to those who would most benefit from it. Initially these investigations were carried out on patients cared for by the academic unit, but with increasing acceptance and cooperation from consultant colleagues, all patients attending the GRMH were included.

CHAPTER 2

THE OBJECTIVES OF THE THESIS AND GENERAL METHODOLOGY

Since 1980, the author has initiated a programme of clinical and scientific assessment of the hypertensive patient in the Glasgow Royal Maternity Hospital. He has assumed the role of "research director" in the initiation and development of this programme, raised the necessary research money and engaged research fellows to undertake the studies primarily designed and selected by himself. Some of these projects were developed further by these fellows some of whom have obtained secondary degrees. The programme is continuing and some of the projects are incomplete and will be reported in due course in scientific journals. They will be alluded to in Chapter 11.

This thesis describes the completed clinical and research projects conceived, initiated and directed by the author under the following headings.

2.1 A Critical Review of the Current State of Knowledge

Every attempt has been made to review the relevant literature. It was important that new studies should be aimed at answering gaps in the knowledge or clearing up confusion rather than repeating reliable studies already well documented.

This critical review is in separate parts.

1) The **Definition** of pregnancy hypertension.

2) The **Aetiology** of pregnancy hypertension.

3) The **Risks** of pregnancy hypertension to both mother and baby.

4) The current thoughts on **Management** of pregnancy hypertension.

This work is presented in **Chapter 3.**

2.2 Assessment of Risk to Glasgow patients.

Although the risks of pregnancy hypertension in general are described in Chapter 3, it was important to investigate the current risk to patients attending the Glasgow Royal Maternity Hospital (GRMH) as treatment protocols would be directed at this group of patients.

The GRMH has been at the centre of Glasgow Obstetrics for 150 years. Over 550,000 Glaswegians have been born within its walls and an similar number delivered within its districts. It would appear to be a perfect place to study the changing incidence of a condition over time and its concomitant risks. The medical records are available in some form going back over 50 years. Some of the records themselves are accessible and the hospital reports also give full information on the problems of each year. It was decided to use eclampsia as a marker of disease change over time as it is a hard end point where the accuracy of the diagnosis over time would not be questioned.

The questions that were asked were:-

1) What is the change in the **incidence** of eclampsia?

2) Has there been a change in the **presentation and timing** of eclampsia?

3) Has there been a change in the **outcome** for the mother and baby?
4) What have been the changes in the **management** of the condition?
5) What **pointers** can be found for the development of management protocols.

This work is presented in **Chapter 4.**

2.3 Studies on disease presentation and diagnosis.

Little in obstetrics has been studied or assessed by randomised clinical trial (Yusuf, Collins and Peto, 1984). Antenatal care, blood pressure measurement, weight estimation and clinical examination all were established at a time when widespread maternal and fetal death was a recent memory. In many parts of the world, it is still a fact of obstetric life. However, it is now accepted that many patients presenting with hypertension in pregnancy are not at major risk, and that the outcome for the mother and baby of hypertension in pregnancy is no worse than in the normotensive patient, unless severe disease occurs. If it were possible to distinguish the low risk from those who may progress, it might be possible to attenuate the progression to the more severe form and so reduce the risks to mother and fetus. It would also allow the low risk patients to be treated as normal pregnancies, reducing the chance of obstetric interference.

Modern obstetrics has given the obstetrician a wide armoury of tests and equipment for monitoring the wellbeing of the mother and her fetus. Many of them are expensive to use in equipment cost and staff. These techniques are not particularly transportable to other centres with fewer resources. Many have not been fully evaluated and are accepted because they are 'clever' rather than because they are useful. Tests that are associated with a given disease state might be useful in the study of the aetiology, but may be of little value if they add nothing to the clinical evaluation of the condition. The aims in this thesis were to study the various routine tests available and choose the simplest that would give the most useful information.

The questions asked were:-

1) How **accurate** is the measurement of blood pressure?
2) What is the normal **variation** in blood pressure measurement throughout pregnancy?
3) Which of the 'routine' tests give the best information concerning disease **diagnosis** and **progression**?
4) How many women **progress** from a mild form to a severe form of the condition?
5) Can signs of disease progression be found and be used as an accurate disease **predictor**?
6) Can the patient be **categorised** into a **low risk group** to be allowed to return to normal antenatal care?
7) Can simple **protocols** be drawn up for the investigation of a hypertensive patient and implemented easily on an **outpatient** basis?

This work will be presented in **Chapters 4-7.**

2.4 Aetiology of pregnancy hypertension

The aetiology of this condition is still largely unknown. Although it could never be hoped that this work would answer this perplexing problem, there were certain areas that were investigated closely to try and increase the understanding of the causes of the condition. It was hoped that this might help design potential management protocols.

As will be discussed in the review chapters, one of the most persistent findings in preeclampsia is platelet consumption. This may be part of the disease process or caused by it. Studies were carried out into the incidence of platelet consumption and its relationship to disease progression.

The questions asked were:-

1) What are the changes in **mean platelet volume** in hypertensive disease in pregnancy?
2) Do the changes demonstrate signs of **platelet activation**?
3) When does **platelet** activation take place and does it **antedate** the presentation of the clinical signs?

This work was based mainly on changes in platelet size and will be described in **Chapter 8.**

Control of platelet activation involves the prostaglandin system. Abnormalities of prostacyclin/thromboxane balance may be responsible for any abnormality of platelet function. Another abnormality that has been found in preeclampsia is vascular reactivity. Prostacyclin is a potent vasodilator and thromboxane is a vasoconstrictor. Therefore, an imbalance of prostacyclin/thromboxane balance may be responsible for these vascular findings. Therefore, studies of the blood levels of the metabolites of prostacyclin and thromboxane were carried out in normal and abnormal pregnancy. The assay work was carried out at the authors request by the University Department of Medicine in the Glasgow Royal Infirmary. An integral part of these studies was the development of the assay techniques. These have been published (McLaren *et al.*, 1985) and will only be commented on in the methodology sections and the discussion.

4) What are the normal changes of **prostacyclin** and **thromboxane** metabolite levels in normal pregnancy?
5) What **changes** are seen in patients with preeclampsia?
6) What is the **timing** of these changes?

This work will be described in **Chapter 9.**

2.5 Treatment of the condition

Delivery of the preeclamptic patient is the mainstay of treatment, as it leads (eventually) to the cure of the patient. Traditionally medical therapy has been restricted to the use of anticonvulsants and the acute use of antihypertensive drugs in severe hypertension. At the time of commencement of this work, studies were

beginning to report the benefits and the harm of antihypertensive drugs in pregnancy hypertension. Over the time of this work, newer drugs have become available. These have allowed a wider investigation of the role of blood pressure lowering drugs.

The questions asked were:-

1) Are **antihypertensive drugs** effective in pregnancy?
2) How do they compare with **traditional bed rest**?
3) What effect do they have on the **disease process**?
4) What **side effects** are seen in the mother?
5) What effect do they have on the **fetus**?
6) What patients, if any, **benefit** from therapy?

This work will be described in **Chapter 10.**

2.6 Project goals

The project goals were:-

1) To try and gain a **greater understanding** of how the disease **develops**, **progresses** and how it **causes its harmful** effects.
2) To increase the **monitoring** for patients at particular risk.
3) To reduce the **mortality and morbidity** especially for the baby.
4) To clarify the role of **antihypertensive drugs**.
5) To develop a **logical and individual approach** to the management of the condition.

These objectives will be taken in turn and **Chapter 11** will discuss whether any of the project goals have been met.

2.7 General Methodology.

Methodology will be discussed in each chapter where it is relevant but there are some general methods used which will be outlined here.

The patient population

In any study of incidence and management, it is important to study a 'total' population. This prospective investigation of hypertension in the Royal Maternity Hospital in Glasgow was based on all the patients presenting to the hospital from January, 1981 until December, 1989. The patients were seen on admission to hospital or at attendance at the Daycare Assessment unit by the author or by one of the hypertensive team. The records department also provided lists of all patients who were coded as hypertensive and this was checked against our records. Computerisation of the Daycare attenders and the admitted patients was carried out to allow full analysis of the total patient group. As will be discussed in Chapter 3, preeclampsia is thought to be mainly a disease of the primigravida. Therefore studies of aetiology and monitoring were confined to primigravidae. Management studies also included parous women, but the patient groups will be clearly documented.

The Hypertensive team

The work with the hypertensive patients was conceived, initiated and directed by the author. However, with the increasing work load, help was required. As part of the expanding research programmes, grants were obtained and a series of research registrars were appointed. These registrars helped form the 'Hypertensive Team'. All the hypertensive patients were seen on admission by a member of this team. The members of the team reported directly to the author. There was a weekly team meeting when all the outpatient and inpatient problems were discussed. This allowed all the studies and management protocols to be coordinated.

Developing protocols

The main aims of this thesis was to study the aetiology, presentation and progression of hypertension in pregnancy. However, various treatment regimes were also developed. All were designed and altered by the author and are described in **Chapter 10.**

The development of a microcomputer database.

There has been much interest in the use of computers in obstetrics, mostly using mainframe or minicomputers with the ability of collecting and storing large quantities of information. These systems are expensive and controlled by hospital administrators. Because of this, the design of the database is largely orientated towards the administrators' needs. There is little clinical data except the basic information concerning antenatal visits and birth details. Although this information is important to collect, it has little value to the clinical researcher with a specific area of interest. Large systems are inflexible, have relatively fixed databases and limited access points. Often only a few terminals can be active at any one time and the access time is limited during office hours when demand is highest. The advantages of microcomputers is that they are cheap, locally controlled, and data handling is more flexible and can be tailor made to the needs of the user. A microcomputer can be linked to mini's or mainframes to transmit or collect information, and to laboratory and clinical equipment to collect 'hands off' data. Its use can be variable, as it can be used for different databases, as a word processor, spreadsheet or statistics calculator.

As part of the development of the projects into the study of hypertension in pregnancy, it was important to develop computerised data collection systems to allow accumulation of patient information and results to ease analysis and followup. All this work was carried out personally by the author. The first area computerised was the Daycare Assessment Unit for high risk pregnancies. The microcomputer was used to collect and display the information in 'real time' in the unit itself. The computer calculated the average blood pressure readings. On screen,

all abnormal results were highlighted in red to make sure that they were not missed. At the end of the day, a printout of the data was produced for insertion into the case notes for a permanent record of the attendance. The data was stored on disc to allow calculation and study of the data on a regular basis.

Equipment used

The equipment that suited this purpose best was the BBC 'B' microcomputer, despite its recognised limitations. It was fast, had good graphics, fast disk access and could easily be interfaced with other equipment. A further advantage of the system was that it can be relatively easily programmed. The necessity of this became increasingly obvious when it was realised that few commercial systems allowed the freedom of data input, analysis or display that we desired. Although commercial packages such as Dbase and Viewstore are useful, a specific database system was developed allowing a custom designed 'front end', display and statistical programmes. These files could be transferred into Viewstore or Dbase compatible files to allow manipulation of the data via the commercial packages but it was not necessary to have these programmes in the machine to use the system.

Methods

The initial equipment of a BBC microcomputer, twin disk drive, monitor and printer cost less than £1,000 and gave word processor as well as database facilities. A programme was written in BASIC to collect the data in 'real time' (see Appendix). Care was taken to make sure the data was verified at input. The programme was menu driven (Fig. 2.1) and required no computer experience to use. Student midwives were competent in using the system within the first day of being in the unit. All the information was in numerical form or from a choice list, no free text was allowed. This helped to confine the information to the expected values for analysis. The information was stored immediately on disk, so even if the system crashes, all information is retrievable. Data was backed up weekly and indexed under patient name, number and date of attendance, allowing easy access to stored data. The file was compact so that one year's visits or 2,000 attendances could be stored on one side of a floppy disk as one file. This is approximately 276 Kilobytes. The information stored is shown in Table 2.1. All this information was known on the day of attendance. The average blood pressure, uric acid and platelet count were used for patient assessment as described in Chapter 7. At the end of the day the information can be displayed on screen for analysis (Fig. 2.2) and printed out for case records (Table 2.2). At the end of each week summary sheets were printed of patients belonging to a specific consultant or specific results value (e.g., platelets between 100,000 - 200,000). This information was assessed by a separate access programme. Further equipment was purchased because of increasing demands for data storage.

Initially this was more BBC microcomputers but as prices of computer equipment began to fall, IBM compatible machines were used with the Dbase 3+ database programme and then Macintosh equipment with FileMaker Pro, Foxbase, Statworks and Cricket Graph programmes. All data collected on any machine can easily be transferred to any other machine to allow full analysis and display.

All the systems have been developed 'in house'. There is now 6 years of data on Daycare attendances allowing analysis of daily, weekly and monthly attendances, number of new patients and return visits, serial results for any patient and selection by data group. Inpatient and followup data have also been collected on separately developed systems.

The connection of a BBC microcomputer to a Dinamap blood pressure recorder for collection of 'hands off' blood pressure data.

As part of the blood pressure studies, the automatic blood pressure machine, Dinamap, was used. This work is described in **Chapter 5**. To aid data collection, the Dinamap was connected to the computer to collect 'hands off' data. It was hoped that this system would eventually help to reduce the nurses' workload.

BBC/Dinamap Interface

The BBC has multiple interface ports. The Dinamap has various outputs of its BP and pulse readings, either from the printer port or a 'standard' RS232 port. The BBC RS423 domino socket was used to connect with the Dinamap. With the original Dinamap the printer output was easily used, but with the newer Dinamaps the information is transmitted at 600 BAUD from the RS232 output and the BBC can only read this data if there is a software alteration in clock time readings. This can be done by a specific 'FX' call. The information is presented as a stream of ASCII characters, giving BP, pulse and machine estimated mean arterial pressure (MAP). These are read from the RS423 input buffer and the components split into their separate parts. The information is stored on disk and displayed in graphical form in colour and in numerical form. An average blood pressure and pulse are updated after each reading. The graphical display is in 'bar' format, the scale is self-correcting but starts with a range between 150 and 50 mmHg. It moves up and down by 10 mmHg as necessary. An arbitrary figure of 90 mmHg diastolic is taken as abnormal and all readings above this are displayed in red. The information on disk is indexed under name, number and date. The average BP reading is transferred to the day care file to allow display of this figure as well the nurses' readings. The Dinamap programme can be used separately as a BP screening method or as part of an 'intelligent' patient monitor.

2.8 Statistics

All statistics carried out were done by standard commercially available packages,

mostly Statworks on the Macintosh microcomputer. The methods used were :-

the **Student 'T' Test** to study differences between the means of groups,

the **Fishers Test** and the **Chi Square Test** to look for differences of the occurrence of events between groups,

the **Wilcoxon Rank Sum Test** to investigate within patient changes,

the **Spearman Test** of correlation was used to investigate the association between various parameters and

multivariant regression analysis was used to study the independent relationship between parameters. A **stepdown procedure** was used to check the validity of the significant results. This involves the removal of the non-significant results in a stepwise fashion until only the significant results are left. Advice was gratefully received from Dr Pravn in the University Department of Statistics.

The thesis was typed and all graphics were done by the author using MacWrite II, Cricket graph 1.3 and MacDraw II on a Macintosh microcomputer and printed on a LaserWriter IINT.

CHAPTER 3

A Critical Review and Discussion of the Old and Current Literature

3.1 The Definition of Pregnancy Hypertension

(Lat. Definire: to set limits to)

Accurate disease definition is important to allow assessment of the risk that the disease entails and for comparison between investigating centres. It is important to set the limits of the disease groups under study. The definition should be partly related to the aetiology of the condition and partly to the clinical presentation. It is important that the method of defining the problem is easy to implement and is reproducible in any environment without need for specialist knowledge or equipment.

Over 100 different names have been used to define hypertension in pregnancy (Rippman, 1968). This is because the aetiology is largely still unknown and the clinical picture is so variable. If the classification is based on clinical presentation alone it becomes less specific and more like a syndrome than a disease state. Hypertension in pregnancy is largely defined using the main presenting signs of hypertension, oedema, proteinuria and convulsions. More recently 'subdefinitions' have been produced based on laboratory findings. HELLP syndrome (Weinstein, 1982; Weinstein, 1985) consisting of Haemolysis, Elevated Liver enzymes and Low Platelets, is one such example which has done little to 'help' the understanding of the problem (Greer, Cameron and Walker, 1985).

There has been some improvement over the centuries. When Hippocrates first described eclampsia, he did not differentiate it from epilepsy. Similarly, Gabelchoverus, in the sixteenth century, felt that pregnancy was a cause of epilepsy. This is because the clinical presentation of epilepsy and eclampsia can be very similar if other factors such as blood pressure and proteinuria are not taken into account (Chesley, 1980). By the end of the 18 th century, there was a realisation that the condition was specific to pregnancy and the term "Toxaemia" of pregnancy was introduced (Beker, 1948). This further confused the situation as it implied the presence of a toxin causing the condition. Years of fruitless research followed but no toxin has been found despite the recent description of the 'worm' (Lueck *et al.*, 1983a; Aladjem, Lueck and Brewer, 1983; Lueck *et al.*, 1983b; Sibai and Spinnato, 1983; Perkins and Cauchi, 1983). Another problem was that several conditions came under the term 'toxaemia' including hypertension and eclampsia, albuminuria alone, acute yellow atrophy and hyperemesis gravidarum (Munro Kerr, 1933). This makes the interpretation of studies reported from that time difficult. When Lever (1843) and Simpson (1843) found proteinuria in the urine in the 19 th century, they wrongly assigned the blame for the condition to the kidney. It was not until the histological findings of Baird and Shaw Dunn (1933), Sheehan (1950), Sheehan and Lynch (1973) and McCartney (1964) that the separation of renal disease from the preeclamptic

lesion became accepted.

It, therefore, became obvious that there were two main groups with hypertension in pregnancy (Chesley, Annitto and Cosgrove, 1976):-

1) Hypertension occurring for the first time during the pregnancy, labour or puerperium and returning to normal after the end of the pregnancy.
2) Pregnancy occurring in patients with preexisting essential hypertension, renal disease or other hypertensive disease diagnosed by previous history prior to pregnancy, high blood pressure at the booking clinic or persistent hypertension after the pregnancy is over.

The problems do not stop here. What is hypertension ? What is the relevance of the other two main clinical signs of proteinuria and oedema? Where does eclampsia fit into the criteria? If a patient has preexisting disease, is it renal in origin or has the patient essential hypertension? Can such a patient develop 'superimposed' preeclampsia?

What is Hypertension ?

Blood pressure is not an absolute value but a variable physiological measurement. In a large population it forms a normal Gaussian distribution. Pickering (1968) stated that arterial pressure is a quantity and should be treated as such. The diagnosis of hypertension is fairly arbitrary and there should not be a rigid cutoff point taken to diagnose abnormality. Hypertension is not a disease in itself but a reflection of an individual's response to an underlying stimulus. It can therefore be used as a marker of risk. Obviously, in any disease situation, the risk that a given value produces is an important parameter in determining whether that value is abnormal or not. It should be remembered that discovery of an association of high blood pressure and a detrimental outcome does not imply cause, only a relationship.

Studies by Friedman and Neff (1975) and Page and Christianson (1976) suggested that the risk to the baby increased significantly once the diastolic blood pressure was above 95 or 90 mmHg respectively (Table 3.1). Friedman and Neff (1975; 1976; 1978) found that this was true at all gestations. This finding is surprising. In many women, the diastolic blood pressure rises to above 90 mmHg as they approach term when blood pressure reaches prepregnancy levels. These patients are at low risk of fetal loss (MacGillivray, 1961; Friedman and Neff, 1978). These studies confirmed the findings of the British Birth Survey of 1958 (Butler and Bonham, 1963, Butler and Alberman, 1969) that a single diastolic blood pressure above 90 mmHg was associated with an increased perinatal mortality rate. However, the more recent British Births Survey 1970 (Chamberlain *et al.*, 1978b) did not demonstrated this, as a rise in perinatal mortality rate was not associated with diastolic blood pressure until it was either above 110 mmHg, or above 90 mmHg with significant proteinuria (Table 3.2). Similar findings were seen if the end point was neonatal neurological

complications. The report concluded that raised arterial pressure in pregnancy, whether due to preexisting hypertension or to preeclampsia, increases the risks that the fetus will grow poorly, die in utero or be delivered prematurely (Chamberlain *et al.*, 1978b). This would appear to be an over statement from their data as it would seem that in the absence of severe disease, the outcome is no worse than in the normal population. Differences in the outcome of pregnancies between these studies may well be due to management variations rather than disease disparity.

The risks to the mother are more difficult to assess. Pregnancy hypertension is one of the largest causes of maternal death in England and Wales in the last twenty years. Cerebral vascular accident (CVA) was the commonest mode of death in this group (DHSS, 1969; DHSS, 1974; DHSS, 1979; Turnbull, 1987; Turnbull *et al.*, 1989; Scottish Home And Health Department, 1978; Scottish Home And Health Department, 1987; Scottish Home And Health Department, 1989). It was often difficult to discover the maternal blood pressure before this event occurred as many patients presented only after the occurrence of the CVA. It can, however, be assumed that the risk is associated with a rise of blood pressure to abnormally high levels for that given patient. Blood pressures of 170-180/110-120 mmHg or greater are equivalent levels to those that produce vascular damage in experimental animals (Goldby and Beilin, 1972). The association with other complications is not so clear.

In many studies there has not been an absolute correlation between blood pressure rise and eclampsia. Cruickshank (1927) in a review of patients in the Glasgow Royal Maternity Hospital, showed that 18.5% of the eclamptics had a systolic blood pressure below 140 mmHg. In the John Hopkins Hospital between 1924 and 1943 in 2,418 cases of preeclampsia only 92 (3.2%) of the patients developed eclampsia (Chesley, 1971). Therefore, the risk of eclampsia would appear to relatively low for the preeclamptic.

In the 1930's, over 75% of all cases of abruptio placenta were associated with preeclampsia (Munro Kerr, 1933). More recent studies suggest that that is no longer true since now more than two thirds of the cases occur in patients with normal blood pressure (Chamberlain, 1981). Although the British Birth Survey 1970 shows a slight increase of abruption in hypertensive patients (1.38%) compared with normotensive patients (1.05%) (Chamberlain *et al.*, 1978b), there was no increase in the perinatal mortality rate in these cases unless the abruption accompanied severe hypertension. Again, hypertension should not be classified as a risk factor for abruption.

Therefore, in summary, **diastolic blood pressure of above 110 mmHg appears to increase the risks of morbidity and mortality particularly to the mother** and can be taken as abnormal meriting some form of management decision. **A diastolic blood pressure above 90 mmHg may constitute a slightly increased risk especially in the**

presence of proteinuria but this risk is mostly to the fetus implying the need for increased monitoring.

The absolute level of blood pressure measured may be less important than the absolute rise and the temporal aspect of that rise. Some workers believe that a rise of blood pressure of 30/20 mmHg to whatever level is sufficient for a diagnosis of preeclampsia (Chesley, 1978; Zuspan, 1966). Redman states that the sudden increases of blood pressure that occurs in severe preeclampsia and eclampsia are the most likely cause of the associated neurological signs and cerebral pathology (Redman, 1980).

Therefore, a rise in diastolic blood pressure to levels above 90 mmHg would appear to put a patient into an 'at risk' group. A diastolic BP of above 110 mmHg would signify a more severe risk, particularly to the mother. It would be reasonable to use these measurements as differential markers of disease severity. If the rise in the blood pressure has been acute, the risk is consequently higher. However, it is important to remember that maternal risk does not necessarily represent a fetal risk and the risk is not absolute as most of the patients will have a successful outcome.

Blood Pressure Measurement

All these studies presume that the measurement of the blood pressure is accurate. Some workers take one reading only to classify the patients. There is a wide degree of inherent variation in the blood pressure itself (Munro Kerr, 1933; Pickering, 1968; Redman, Beilin and Bonnar, 1977a). There is also a variation found in the methodology and it is probably important to standardise the method of measurement to allow comparison between centres (O'Brien; and O'Malley, 1979). In the non-pregnant patient the fifth Korotkoff sound corresponds to the intraarterial measurement (Kirkendall, 1967). However, in pregnancy, the fifth sound may continue down to zero because of the hyperdynamic circulation, and the fourth Korotkoff sound is more reproducible (MacGillivray, Rose and Rowe, 1969) This is taken by most centres to measure the diastolic blood pressure in the pregnant woman. Many of the older studies used the fifth sound and this is still recommended in some texts. This often leads to false comparisons, as obviously more patients will have a diastolic blood pressure over 90 mmHg if measurement is by the fourth sound rather than by the fifth sound.

MacGillivray (1961) in his study of blood pressure throughout pregnancy showed that there was no difference in the diastolic blood pressure with the patient in the lying position or sitting at an angle of 30-45 degrees from the horizontal (Fig.3.1) (MacGillivray, 1961). The blood pressure should be taken in the right arm with the sphygmomanometer at the level of the heart. The patient should be rested prior to the measurement. The practice of lying the patient on their left side to rest and then

taking the blood pressure in the right (upper) arm, can produce a BP that is falsely low by as much as 15 mmHg because of the hydrostatic pressure differences between the sphygmomanometer cuff and the heart.

Most workers use a **single diastolic blood pressure reading above 110 mmHg as being adequate for a diagnosis** of severe preeclampsia (Hughes, 1972; Nelson, 1955b; Gant *et al.*, 1980). For the diagnosis of mild or moderate hypertension, **two readings above 90 mmHg diastolic at least 6 hours apart are accepted.** It is important that these readings are close enough together to imply a definite relationship (Nelson, 1955b).

Proteinuria

The definition of "proteinuria" depends on the methods used. Protein excretion goes up in pregnancy from a level of around 18 mg in 24 hrs in the non-pregnant to over 300 mg total protein. Albumin represents about 55% of this. The Committee on Terminology of the American College of Obstetricians and Gynaecologists recommend that a total daily protein excretion over 300 mg should be taken as abnormal (Hughes, 1972). When 'dip' sticks are used, the false positive rate is around 25% with 'a trace' and 6% with 'one +' . This is probably due to the fluctuation in the concentration of protein in the urine and the presence of vaginal contamination or urinary infection. Therefore, if proteinuria is suspected, 24 hour urine collections should be made.

The importance of proteinuria has been known since the 19 th century but renal disease was initially not differentiated from preeclampsia. Nelson in his clinical study of preeclampsia (Nelson, 1955b) used the presence of proteinuria as his main differentiate of mild and severe disease. Friedman and Neff (1977), in their study of over 32000 pregnancies, showed that proteinuria is associated with increased perinatal mortality even in the absence of hypertension (Table 3.3). Unfortunately they defined hypertension as blood pressure above 95 mmHg diastolic. It is possible that some of these proteinuric non-hypertensive patients had a diastolic blood pressure of above 90 mmHg and would be defined by many as preeclamptic. In the same patient group, they showed that, in combination with hypertension, proteinuria increases the risk of perinatal loss, neonatal cerebral signs and intra uterine growth retardation (Table 3.4) (Friedman and Neff, 1975). It is difficult to explain why proteinuria is associated with this increased risk to the fetus. It is almost always associated with the 'pathognomonic' preeclamptic glomerular lesions (Fig 3.2) (Sheehan and Lynch, 1973). Rather than being associated with a worsening disease risk, it may be that the presence of proteinuria increases the probability of the patient having 'true' preeclampsia. The risk to the fetus is therefore higher because the pregnancy is complicated by preeclampsia rather than 'simple' hypertension.

Although proteinuria is associated with increased risk to the baby, there is less evidence that it is associated with an increased risk to the mother. Gibberd is quoted as presenting a series 300 patients with albuminuria out of 8000 pregnancies (Gibberd, 1928). Only 3.7% of these patients developed eclampsia. These results are similar to those found with raised blood pressure alone. However, the few maternal deaths seen in the United Kingdom are almost always associated with proteinuric hypertension. This again may be due to the presence of proteinuria confirming the diagnosis.

These studies suggest that the presence of proteinuria implies a specific renal lesion confirming the diagnosis of preeclampsia. It is associated with an increased risk to the fetus of both IUGR and death. The effect on the risk to the mother is less clear but it is an obvious sign that increased vigilance is required.

Oedema

Oedema is a common finding in normal pregnancy. 64% of normal women have oedema of the face and hands (Dexter and Weiss, 1941)and this is associated with no adverse affects (Chamberlain *et al.*, 1978b; Dexter and Weiss, 1941) Although Hamlin (1952) reported oedema in the fingers of almost every primigravida who developed PIH six weeks later, the additional presence of oedema does not increase the risk of hypertension (MacGillivray and Campbell, 1980).

Conclusions

Therefore, although hypertension in pregnancy is indeed polysymptomatic, high blood pressure is the primary sign of danger to the mother. Proteinuria is significant as a risk factor to the fetus and oedema appears to have no significance at all. It would seem reasonable to classify the problem for the mother on the basis of hypertension and the fetal risk on the presence of proteinuria or some more specific method of fetal monitoring.

There is one further problem in the definitions of hypertension in pregnancy, and that is the role of parity.

Parity

'Pure' preeclampsia is defined by Nelson as a diastolic blood pressure over 90 mmHg with proteinuria of over 300 mg in 24 hours occurring in a primigravid patient where there is no evidence of preexisting hypertensive disease (Nelson, 1955b) This definition is widely accepted and was validated by the biopsy studies of McCartney (1964). This study showed that the majority of primigravid patients with proteinuric preeclampsia had the pathognomonic renal lesion (Fig 3.2). However, the results also showed that although most of the multigravid patients with proteinuric disease had underlying renal disease, some patients did have the classic renal lesions. Therefore, the diagnosis of pure preeclampsia is more likely in primigravidae but it cannot be

excluded in a later pregnancy (McCartney, 1964). If it does occur it tends to be less severe (Table 3.5). Therefore, multigravid women are unlikely to develop the disease for the first time but the diagnosis of preeclampsia is still possible. If a patient has preeclampsia in her first pregnancy, she is more likely to have problems in her next pregnancy (Table 3.6). However, if apparent "mild preeclampsia" is found in a multigravid patient, the patient may be demonstrating a tendency towards 'latent' hypertension which recurs in subsequent pregnancies and she will have an increased chance of developing hypertension in later life. Such women often have a strong family history of essential hypertension (Chesley, 1980; Nelson, 1955b; Chesley, 1978; Gibberd, 1928). Nelson, in a study of 5251 booked married primigravidae between 1948-1953, showed that this 'latent hypertension' increased in incidence with increasing age (Fig 3.3) (Nelson, 1955b). This was not true of 'pure' preeclampsia. Proteinuric hypertension occurring for the first time in pregnancy in a primigravid patient is almost certainly preeclampsia. To be surer of this diagnosis, postpregnancy followup is also required to make sure that normality returns.

Therefore, if a "pure group" is to be studied for the aetiology of preeclampsia, a primigravid proteinuric group should be chosen.

Although preeclampsia can occur in the multigravid patient, the diagnosis is less accurate. Mild or moderate preeclampsia will often be confused with latent or essential hypertension in any pregnancy.

In order to study the effect of therapy, all groups can be investigated. However, care should be taken to separate them into their component groups prior to study as they may differ in their responses to treatment.

Eclampsia

Eclampsia can be defined as a convulsive state occurring during pregnancy associated with hypertension prior to or after the fit has taken place. Although eclampsia is often associated with severe preeclampsia as the name suggests (Hamlin, 1952; Dawson, 1953) this is not always so. Convulsions may occur in the presence of mild preeclampsia and most severe cases of preeclampsia are not complicated by eclampsia (Cruickshank, 1923; Nelson, 1955a). The seizure threshold of the patient probably has as much to do with the occurrence of the seizure as the hypertension (Nelson, 1955a; MacIntosh, 1952). In Nelson's studies (1955b; 1955a), all the baby deaths associated with eclampsia occurred in patients with severe preexisting preeclampsia, and none in the patients where the preexisting preeclampsia was mild. In fact, **he states that a case of eclampsia occurring with mild preeclampsia was probably less dangerous to mother and baby than a case of severe preeclampsia with no convulsions.** The grading of the patient should be related to preexisting preeclampsia rather than an automatic inclusion in the severe group or a

separate group (Nelson, 1955a).

Preexisting Hypertensive Disease

Once it was accepted that young women could have essential hypertension it was realised that renal disease was not as common as once thought. If the blood pressure was known to be elevated prior to pregnancy, the diagnosis of preexisting hypertension was obvious. However, as most patients presenting in their first pregnancy will probably never have had their blood pressure checked before, this may not be known. If the blood pressure is found to be elevated in the first half of pregnancy, a diagnosis of preexisting hypertension can be assumed. But since the diastolic blood pressure may fall by as much as 15 mmHg in the second trimester (MacGillivray, 1961), a diastolic of 85 mmHg at 16 weeks may hide a nonpregnant equivalent of 100 mmHg. This patient may have been diagnosed correctly if she had presented earlier in the pregnancy. Therefore, only a normal first trimester blood pressure can be used to exclude essential hypertension accurately. With the rise of blood pressure towards term, a false diagnosis of preeclampsia may be made if the diastolic rises over 90 mmHg on its way back to prepregnancy levels (MacGillivray, 1961). Many of the 'latent' hypertensive group probably fall into this category. If the blood pressures remain in the mild to moderate range, this will have little clinical relevance but would interfere with any 'pure' group studies.

Most patients with renal disease are known prior to pregnancy but the differentiation between renal disease and essential hypertension has been made easier with the development of methods of assessment of renal function. The presence of proteinuria in early pregnancy should alert the obstetrician to possible renal problems which can be confirmed by plasma creatinine estimation, urinalysis for infection and casts, and ultrasound of the kidneys.

'Superimposed' preeclampsia

This is described as an exacerbation of hypertension or the development of proteinuria in previously observed hypertension or a rise in uric acid to high levels in a patient with known essential hypertension (Redman, Beilin and Bonnar, 1977b). These criteria are useful in cases of essential hypertension but it is more difficult to differentiate 'superimposed' preeclampsia from a deterioration in renal disease. Whatever the reason for the worsening of the underlying cause of the hypertension, the risk to both the mother and the fetus is significantly increased (Chamberlain *et al.*, 1978b).

Conclusions

It is clear that there are major problems in the clinical diagnosis of hypertension in pregnancy. **Proteinuric hypertension, occurring for the first time, in a primigravid pregnancy can be accurately diagnosed as preeclampsia. All other forms of**

hypertension could be due to other aetiologies.

Even if a diagnosis can be made, there is a further complication of disease nomenclature.

Nomenclature

Over the years many names have been used to describe hypertension in pregnancy (Rippman, 1968). Although much effort has been made to simplify the problem, the situation is still confused.

The Organisation Gestosis was set up to attempt to clarify the diagnosis. Since they decided to use a symptomatic method of nomenclature based on oedema as the cardinal sign (Table 3.7), their recommendations have not been universally accepted. The full name of their condition is EPH-Gestosis using the signs Edema, Proteinuria and Hypertension as the method of diagnosis. Each sign is classified numerically according to the severity and the diagnosis is made. e.g. $E_1P_2H_2$-Gestosis for a patient with mild oedema, moderate proteinuria and moderate hypertension. The method is simplistic and relatively reproducible and transferable. Its main drawback is the importance placed on the oedema. The presence of oedema and proteinuria constitutes "gestosis" even in the absence of hypertension. There is also a further category of 'imminent' eclampsia.

The other main international group studying hypertension in pregnancy (The International Society for the Study of Hypertension in Pregnancy or ISSHP) concentrates on hypertension as the main diagnostic factor along with proteinuria but ignores the presence of oedema (Table 3.8) (Davey and MacGillivray, 1988). This is similar to Nelson's criteria (Nelson, 1955b). This is the most widely accepted nomenclature. It is clear that "true preeclampsia" should be used only for the primigravid patient with no preexisting disease who develops proteinuric hypertension in the second half of pregnancy. This would imply that hypertension occurring in pregnancy without proteinuria is not preeclampsia but some other kind of "pregnancy induced hypertension". This is unlikely to be true. Some of the primigravida, with nonproteinuric hypertension, will also have preeclampsia. Moreover, preeclampsia can exist in the multigravid patient, although its diagnosis is less sure. In these situations, the term Pregnancy Induced Hypertension (PIH) is generally used. The main criticism of this term is the implication of aetiology which is unproven. Pregnancy Associated Hypertension (PAH) is a similar term without the aetiological suggestion. "Gestational hypertension" is the same as "latent" hypertension and implies late onset mild to moderate PIH in a multigravid patient. The assumption is that the patient is demonstrating a hypertensive tendency which will become apparent in later life (Nelson, 1955b; Chesley, Annitto and Cosgrove, 1976; Dieckmann, 1952).

Despite the simplification of the classification it is often difficult to define the condition at first presentation. All forms of definition include an unclassified group of patients who present too late or are "unbooked" at the time of admission making accurate diagnosis impossible. Also, many patients classified under one group may need to be reclassified as pregnancy continues since the condition may worsen or preexisting disease may become apparent after delivery.

Discussion

All these problems of diagnosis and nomenclature are only relevant if "pure studies" are required for study or comparisons are to be made between groups. For this reason, all aetiological studies on preeclampsia are generally limited to proteinuric hypertension, occurring for the first time, in a primigravid pregnancy. All other patients can be grouped together as pregnancy induced hypertension unless preexisting disease is known. However, trials of management must be open to all patients as that is how the disease presents to the clinician.

If it is difficult to diagnose and name the condition, studies of aetiology must be reviewed with a healthy skepticism. If there are many disease types, there may be multiple aetiologies.

3.2 The Aetiology of Pregnancy Hypertension

"In summing up this section, it is evident that the cause of eclampsia has not been discovered, and that the peace of mind of all concerned would have been increased, had many of the so-called contributors never written, or at least had withheld their contributions sufficiently long to subject them to ordinary self-criticism."

Whitridge Williams (1931)

In order to understand the disease process and the relevance of the clinical signs at presentation, it is important to understand the aetiology of the condition. If the aetiology were elucidated, early diagnosis and potential prevention may be possible. Unfortunately, in hypertension in pregnancy the aetiology is still largely unknown. There has been much confusion over the role of many pathological findings in this condition. It is important to distinguish the signs caused by disease progression from those that are markers of the underlying process. If this can be done and ,if there are recognisable stages in the disease process, it may be possible to use these changes as predictors of patient risk.

Since the 18 th century, when the term 'toxaemia of pregnancy' was first used, it has been known that there was a specific disease of pregnancy which could be characterised by oedema, hypertension, albuminuria and convulsions (Chesley, 1980). Much has been written concerning the aetiology of preeclampsia. The main problem is that many of the theories that have been put forward for the cause of eclampsia describe the pathological features found at end stage disease (Chesley, 1976). **These may be the result of the disease process rather than the cause.**

Hypertension in pregnancy may not lead to eclampsia. Therefore signs found after maternal death from eclampsia may have little relevance to the earlier stages of the preeclampsia.

In 1916, Zweifel first termed it the disease of theories (Zweifel, 1916). Zweifel states that any cause of preeclampsia must explain the following points :-

1) The predisposing influence of nulliparity, multiple pregnancy, hydatidiform mole and hydramnios.
2) Higher incidence in certain geographical areas.
3) Increasing incidence as term approaches.
4) Rarity of repeated problems in subsequent pregnancies.
5) Improvement after death of the fetus.
6) Hypertension, oedema, proteinuria, convulsions and coma.
7) The hepatic and renal lesions.

The predisposing influence of nulliparity, multiple pregnancy, hydatidiform mole and hydramnios

Nulliparity

Until the histological studies in the 1950's and 1960's (Sheehan, 1950; McCartney, 1964; Sheehan and Lynch, 1973) there was no clear method of accurate diagnosis. It was already known that hypertension was more common in the primigravida (Nelson, 1955b; Munro Kerr, 1933; MacGillivray, 1961) but the renal histological studies showed that the majority of the primigravidae with proteinuria had a specific renal lesion while many of the multigravidae were found to have renal disease (Sheehan, 1950; McCartney, 1964; Sheehan and Lynch, 1973). This suggested that preeclampsia is mostly a disease of the primigravida and a normal first pregnancy can be seen to protect the patient from any future preeclampsia (Chesley, 1978). Even an earlier abortion protects the patient (MacGillivray, 1958). However, if the patient changes partner the incidence increases to that of a primigravida. If the patient has had a prior blood transfusion, she is also protected from developing preeclampsia (Feeney, Tovey and Scott, 1977). There is no evidence that blood group incompatibilities or sex of the child make any difference.

All these findings suggest that the condition is associated with the patient's first exposure to certain antigens carried by the fetus. Prior exposure to these antibodies would appear to protect the patient from disease development. This implies an immunological factor in the aetiology of the condition.

Hyperplacentosis

Another factor influencing the development of preeclampsia is hyperplacentosis (Jeffcoatte and Scott, 1959). This may occur with hydatidiform mole, diabetes, multiple pregnancies, erythroblastosis fetalis and tripliody. Polyhydramnios has also been suggested as a risk factor but the association of polyhydramnios in the absence of other accepted risk factors is probably unlikely (Jeffcoatte and Scott,

1959). Polyhydramnios due to fetal abnormality alone is not associated with a higher incidence and is only associated with preeclampsia if there is another influencing factor involved (Desmedt, Henry and Beischer, 1990). Diabetic pregnancies have a higher incidence of the disease especially if there is poor control (Siddiqi *et al.*, 1991). Hydatidiform mole is associated with classic preeclampsia and eclampsia, but it rarely develops before 16 weeks (Page, 1939; Chesley, Cosgrove and Preece, 1946). Twins are reported to carry a four fold increase in incidence compared to singleton pregnancies. However, there is no difference in the incidence between monozygotic and dizygotic twins (Campbell, MacGillivray and Thompson, 1977). Therefore, it would appear that it is the presence of the placental tissue rather than polyhydramnios that is associated with preeclampsia. This again suggests an immunological basis to the disease as both molar and multiple pregnancy will produce a higher immunological load than normal pregnancy.

Immunological factors

These findings suggest that immunological factors may be involved with some form of maternal and fetal incompatibility producing an abnormal immunological response. This may be due to an imperfect maternal response to pregnancy which improves in the next pregnancy or an inability to recognise paternal antigens displayed by the fetus. The first pregnancy would then help to 'immunise' the patient for any future pregnancy to the same partner (Sutherland *et al.*, 1981). If this is true, there may be differences found in immunological investigations. No increase in ABO, HLA or Y-linked compatibility was found in couples with a preeclamptic pregnancy by Scott and Beer (1976). Redman *et al* (1978) showed a higher incidence of HLA homozygosity. This would reduce the chances of antigen sharing by preeclamptic women and their husbands. They postulate that maternal recessive immune-response genes contribute to the development of preeclampsia (Redman *et al.*, 1978). Therefore, there is evidence of an immunological abnormality in preeclampsia interfering with the normal maternal response to her fetus, but the mechanism is still obscure (Petrucco, 1981). The abnormality may be either an increased response to fetal antigens or a reduction in the suppressive effect normally seen in pregnancy. The greatly increased incidence of preeclampsia in twin pregnancies without any difference between monozygotic and dizygotic pregnancies (Campbell, MacGillivray and Thompson, 1977) suggest increased immune-response suppression rather than increased maternal-fetal incompatibility.

It has been postulated that blocking antibodies are formed by the reaction of the mother to trophoblastic tissue. These antibodies then suppress T-lymphocyte activation (Currie and Bagshawe, 1967). Schmorl and Veit showed the presence of placental villi in the circulation as early as 1933. Therefore, antibody production

would be expected. Insufficient production of blocking antibody could lead an increased maternal immunological activity, placental damage and preeclampsia. However, although circulating antibodies to the placenta have been found in preeclamptic pregnancies (Currie and Bagshawe, 1967), this has not been confirmed by all workers (Currie and Bagshawe, 1967). Various studies have shown complement activation in the placenta (Faulk, Carbonara and Jeannet, 1973; Kitzmiller and Benirschke, 1973) but no definitive findings of immunological damage have been described. There may also be a role for some of the placental proteins, such as PAPP-A, in immunosuppression, as they are known to have an immunodepressant effect (Bischof, 1981).

Therefore, although there is strong circumstantial evidence of an immunological basis to preeclampsia, its exact mechanism and site of action is still unclear. A further complication is that, as will be discussed later, the placental lesion is not specific to preeclampsia. Similar findings are found in intrauterine growth retardation (IUGR) (Sheppard and Bonnar, 1981). This may imply that both the placental lesion and the immunological lesion may not be unique to preeclampsia.

Higher incidence in certain geographical areas.

Differences have been seen between racial groups. In Israel, Jews have a higher incidence than the African or Asian (Table 3.9) However, different geographical incidence of the condition and its severity may be due to environmental differences, particularly diet, and other factors including the standard of health care and the timing of presentation (Davies, 1971). There are also problems with the accuracy of case recording and diagnosis of hypertension in the Third World. Many studies are based on hospital reports which suggest a higher incidence in the urban areas. This could be explained by the differences in the reporting of the condition, in the standard of antenatal care available and the access patients have to medical help.

This makes the assessment of the incidence in racial groups difficult. Despite this, differences obviously exist, and the explanation of this could be related to the environmental and familial factors discussed later (Chesley, Annitto and Cosgrove, 1961; Chesley, Annitto and Cosgrove, 1968; Cooper *et al.*, 1988; Cooper and Liston, 1979).

Increasing incidence as term approaches

The blood pressure rises towards term in most pregnancies (Fig 3.1) (MacGillivray, 1961) and Nelson found that mild or 'latent' hypertension is more common in the later stages of pregnancy (Nelson, 1955b). The epidemiology of hypertension without proteinuria has several characteristic features which suggest that it should not always be regarded as mild preeclampsia (MacGillivray, 1961). The incidence rises sharply over the age of 30 at a time when essential hypertension is also becoming

more common (Fig 3.3) (Nelson, 1955b). The risks to mother and baby of late onset mild to moderate hypertension are much lower when compared with hypertension in pregnancy as a whole (Nelson, 1955a). Mild hypertension occurring during late pregnancy has no depressive effect on fetal growth (Baird, Thomson and Billewicz, 1955). Women who had hypertension without proteinuria were found to have a higher risk of hypertension in later life compared with those with true preeclampsia (Chesley, 1978; Browne and Dodds, 1939). These findings suggest that the finding of an increasing incidence of preeclampsia towards term may be a reflection of the demonstration of the 'latent' hypertension described by Dieckmann (1952), Nelson (1955b) and Browne and Sheumack (1956). This is supported by the lack of pathology, the association with increasing age and the higher incidence of essential hypertension in later life.

Rarity of repeated problems

MacGillivray showed that if the first pregnancy was normal, the incidence in a subsequent pregnancy was low (Table 3.5). If the first pregnancy was complicated by severe preeclampsia, the incidence was found to be similar to that of a primigravida (Table 3.6) (MacGillivray, 1981). The protection in the multipara may be related to the immunological factors previously mentioned. The first pregnancy immunises the woman against her husbands antigens and reduces the reaction. This argument is supported by Feeney, who found that, after a blood transfusion, a woman had a lower incidence of preeclampsia (Feeney, Tovey and Scott, 1977) However, Lopez Ilera followed up 110 patients with a history of eclampsia. In the next pregnancy 35.4% of the patients had repeated preeclampsia although he was less specific in his diagnosis (Lopez Llera and Hernandez Horta, 1974). Therefore, the protection of a first pregnancy is not absolute and appears to be most effective if preeclampsia does not develop. This suggests a degree of susceptibility in those patients in whom the disease is manifest. Therefore, rather than protect against the disease, a normal first pregnancy may 'screen out' those who are not susceptible. This susceptibility may be related to the familial tendencies already alluded to.

Improvement after death of the fetus.

Beker states that "if the foetus dies in utero the general condition of the mother generally improves" (Beker, 1948) However, fetal death is not always followed by immediate clinical improvement. Dexter and Weiss found this in less than one third of cases (Dexter and Weiss, 1941). Therefore, although there may be an improvement, it is not absolute and the susceptibility remains.

Hypertension, oedema, proteinuria, convulsions and coma.

The clinical hallmarks of preeclampsia in the mother are hypertension, proteinuria, oedema and the tendency to convulsions and coma. The physiological

characteristics are an increase in peripheral resistance (Larkin *et al.*, 1980; Lim and Walters, 1979) exaggerated responses to pressor agents (Talledo, Chesley and Zuspan, 1968; Gant *et al.*, 1973; Gant *et al.*, 1980; Zuspan, 1979), activation of the coagulation system (Howie, Prentice and McNicol, 1971), a reduced platelet count (Redman, Bonnar and Beilin, 1978) and decreased uteroplacental blood flow (Lunell *et al.*, 1982). There is also an impairment of the normal increase of plasma volume and cardiac output (Lim and Walters, 1979; Gallery, Hunyor and Gyory, 1979). Before these abnormalities are discussed, a short review of the normal cardiovascular changes in pregnancy will be presented.

Changes in the cardiovascular system in normal pregnancy

Normal pregnancy is associated with a number of alterations in the cardiovascular system which start to occur early in pregnancy. Cardiac output increases by around 40% during the first trimester and this increase is maintained during the third trimester. However, if cardiac output is measured in the supine position a fall in output is noted in the third trimester as the venous return to the heart is obstructed by the gravid uterus. Blood pressure starts to fall in the first trimester, reaches a nadir in mid-pregnancy, then slowly rises during the third trimester to levels comparable with those in the non-pregnant state (MacGillivray, Rose and Rowe, 1969) (Fig. 3.1). As arterial pressure is determined by cardiac output and total peripheral resistance, the decrease in blood pressure must be due to a fall in the latter. Since these changes occur early in pregnancy, they must reflect a change in systemic vascular resistance, as the uteroplacental circulation is not sufficiently large to account for such a reduction in peripheral resistance at this stage of pregnancy.

The fall in peripheral resistance in normal pregnancy is associated with a relative insensitivity to the pressor effects of exogenous angiotensin II (AII) (Fig. 3.4) (Gant *et al.*, 1973), which is detectable as early as 8 weeks gestation and reaches a peak in mid-pregnancy. The mechanism underlying this insensitivity may be prostaglandin dependent. The pressor effects of angiotensin II may be balanced in normal pregnancy by prostaglandin E2 and prostacyclin which have vasodilator effects. It is obvious that changes in these vascular reactivity may be at the centre of the hypertension changes in preeclampsia.

Vascular sensitivity as a cause of hypertension

Beker postulated that 'toxaemia' of pregnancy was not due to a toxin but was related to an upset in the circulatory system (Beker, 1948). Hertig suggested that the disease was one of widespread vasospasm (Hertig, 1945). However, this vascular constriction would only contribute towards the vascular hypertension as the blood flow to the major organs, apart from the uterus, liver and kidney, would continue to be normal

unless there is severe cardiac compromise. There is not a general reduction in peripheral blood flow. Burt showed increased blood flow to the hand and the forearm in preeclampsia, but this may be related to muscle blood flow rather than the true periphery (Burt, 1950). Since that time, there has been much work on the causes of the hypertension. Studies have shown that the vascular system in preeclampsia is hypersensitive to several pressor agents. The first studies used various pituitary extracts (De Valera and Kellar, 1948; Browne, 1946). Browne showed that this sensitivity disappeared after delivery. Raab *et al* (1956) found it with norepinephrine (noradrenaline) and Talledo *et al* (1968), Chesley *et al* (1965) and Zuspan (1979) found it with noradrenaline and angiotensin. Gant *et al* (1973), Wallenburg *et al* (1986) and Deker *et al* (1990) have shown that the angiotensin infusion test can select out patients who are destined to develop preeclampsia by demonstrating sensitivity at 16-18 weeks (Fig. 3.4). This suggests that the sensitivity is present prior to the disease presentation, implying susceptibility to the condition. It is now widely accepted that vasoconstriction is the basic cause of the hypertension in preeclampsia (Gant *et al.*, 1980; Hardy and Williams, 1988; Gilstrap and Gant, 1990). However, since the hypertension develops later in the pregnancy, a further stimulus would seem to be required and the vasoconstriction would then be a secondary effect following this stimulus.

Salt and water retention

Sodium and water retention could be an explanation for the arterial hypertension. Sodium is retained in preeclampsia (Chesley, 1966; Plentl and Gray, 1959). Harding and Van Wyck (1930) gave sodium solutions to preeclamptic women with disastrous results: one patient developed fulminating preeclampsia within 24 hours with a BP rise from 128/100 to 200/140. Dieckmann (1952) showed that a high salt intake in preeclamptic women produced a deterioration of the symptoms and there was a reduced ability to concentrate salt in the urine. However, spironolactone, a drug useful in other salt retaining conditions, has no effect on the blood pressure in preeclamptic women (MacGillivray, 1981). Salt restriction as a therapy is common, particularly in Holland, but prophylactic salt restriction has little benefit on the development of the disease but may have an effect on the sensitivity of the peripheral vasculature by altering AII receptor activity. This has led on to the interest in the renin-angiotensin system.

The Renin-angiotensin system

Salt excretion is controlled by the renin-angiotensin system. As already stated, the response to a angiotensin infusion is abnormal in preeclampsia (Chesley *et al.*, 1965; Gant *et al.*, 1973; Gant *et al.*, 1980). Gant feels that if levels of angiotensin are low, receptor site occupancy will be low and sensitivity to angiotensin will be raised. The

results of studies of blood levels are confusing. Massiani *et al* (1967) found angiotensin levels normal, Weir *et al* (1973) found them severely depressed and Symonds, Broughton Pipkin & Craven (1975) found them to be raised. All the studies were on patients of apparently similar severity.

Both adrenaline and noradrenaline can cause vasoconstriction and increased sensitivity to infusions of these substances have been demonstrated (Talledo, Chesley and Zuspan, 1968; Chesley *et al.*, 1965; Zuspan, 1979) but levels of noradrenaline have been found to be low (Tunbridge and Donnia, 1981).

Broughton Pipkin (Broughton Pipkin, 1976) has demonstrated that the fetal placental unit can produce angiotensin II and the levels in the cord venous blood of babies from mothers with preeclampsia are found to be significantly elevated above levels seen in normal pregnancy. Symonds (Symonds, Broughton Pipkin and Craven, 1975) found that the levels of AII in plasma in late pregnancy in over 50 primigravidae were in direct relationship to diastolic blood pressure. He feels that the fetal placental unit produces angiotensin in response to hypoxia. This, in turn, can produce hypertension in susceptible patients. This production of angiotensin II may act as the trigger. The susceptibility of the patient to respond to this stimulation may be related to prostaglandin activity.

The role of the prostaglandins

There is mounting evidence that the local effects of the prostanoids, prostacyclin and thromboxane, may have a role to play in the pathophysiology of this disease. Prostacyclin (PGI_2) is the major product of the arachidonic acid cascade in vascular tissue, and is a potent vasodilator and inhibitor of platelet aggregation (Moncada *et al.*, 1977; Ritter *et al.*, 1983). It has a short half life and is usually measured as one of its stable metabolites, such as 6-keto-PGF1α. In preeclampsia, production of PGI_2 from both maternal and fetal vascular tissue has been shown to be reduced (Downing, Shepherd and Lewis, 1980; Remuzzi *et al.*, 1980; Jogee, Myatt and Elder, 1983) and lower levels of amniotic fluid prostacyclin compared to normal pregnancy have also been found (Bodzenta *et al.*, 1980; Ylikorkala and Makali, 1985). High levels of prostacyclin stimulating factor have also been found in patients with pregnancy induced hypertension suggesting a reduced end organ response (Remuzzi *et al.*, 1981)

Thromboxane A_2 is a powerful vasoconstrictor and platelet aggregating agent (Ylikorkala and Makali, 1985). It is the major product of the arachidonic acid cascade in platelets, and is synthesised and released when platelets aggregate. Increased TxA_2 production from placentas and platelets has been shown to occur in pregnancy induced hypertension (Makila, Viinikka and Ylikorkala, 1984; Fitzgerald *et al.*, 1990; Walsh, 1989).

Thromboxane A2 and prostacyclin oppose each other through regulation of

adenylate cyclase (Tateson, Moncada and Vane, 1977). The proaggregatory substances thromboxane A_2 and the endoperoxides PGG_2 and PGH_2 inhibit adenylate cyclase allowing free intraplatelet Ca^{++} to rise. They also have a direct effect, promoting Ca^{++} release from intracellular storage sites (Gerrard *et al.*, 1977). Platelet inhibitory prostaglandins stimulate adenylate cyclase, increasing cyclic AMP and reducing Ca^{++} (Tateson, Moncada and Vane, 1977; Gorman, Bunting and Miller, 1977). An increase in intracellular calcium would increase the sensitivity of smooth muscle cells to contract and platelets to aggregate. An increase in intracellular calcium has been found in pregnancy induced hypertension (Kilby *et al.*, 1990).

It has been suggested that normally a balance exists between PGI_2 and TxA_2, and that this balance may be upset in pregnancy induced hypertension (Walsh, 1985). A reduced prostacyclin/ thromboxane ratio would account for the increased platelet consumption and the increasing sensitivity to vasoconstrictors and peripheral constriction found in patients with pregnancy induced hypertension. Experimentally, this increased sensitivity to angiotensin II can be produced in normal pregnancy by the administration of indomethacin, a prostaglandin synthetase inhibitor (Everett *et al.*, 1978).

An imbalance between PGI and TxA could lead to platelet aggregation and the formation of platelet thrombi and fibrin deposition in the kidney and placenta causing impairment of these organs. The renal effects of sodium retention and reduced glomerular filtration rates seen in pregnancy induced hypertension could also be due to the lack of vasodilator and naturetic PGE2 and PGI2 in the kidney.

Therefore, pregnancy induced hypertension could be largely a consequence of a prostaglandin deficiency. This could be either from a deficiency of precursors, reduced production or defective action. O'Brien *et al* (1979) showed that, in pregnant rabbits, a restriction of the dietary essential fatty acid precursors of prostaglandins leads to an increased sensitivity towards angiotensin II. However, studies have shown that only about 50% of the patients sensitive to AII infusions will develop preeclampsia (Gant *et al.*, 1973; Wallenburg *et al.*, 1986) (Fig 3.5). This suggests that PGI_2 deficiency may not be the primary cause of the disease but may play an important role in the pathophysiology of the condition by altering the patients response to vasopressor agents.

Prostacyclin infusions have been used successfully in severe pregnancy induced hypertension (Fidler *et al.*, 1981) where both its vasodilator and anti-platelet effects have been of value. However, PGI2 requires a continuous intravenous infusion and has not been shown to be an efficient antihypertensive agent.

Other prostaglandins have been implicated but the picture is less clear. Demers and

Gabbe (1976) showed that $PGF_{2\alpha}$ was elevated and PGE_2 low in preeclampsia. Hiller and Smith (1981) found no change and Robinson *et al* (1979) found both PGE and PGF to be reduced.

There is no doubt that there is an upset in the prostaglandin biochemistry, most likely to be related to changes in production of prostacyclin. Further work is required but it is unlikely that these abnormalities will be more than a part of the pathophysiological process..

Changes in Rheology

Preeclampsia and intrauterine growth retardation are both associated with abnormal haemostasis which may be related to histological evidence of placental intravascular changes (Bonnar, McNicol and Douglas, 1971; Sheppard and Bonnar, 1976; Brosens, Dixon and Robertson, 1977; Howie *et al.*, 1976). Blood flow, and changes in blood rheology which may reduce blood flow, are important factors in determining the amount of oxygen and nutrients transferred across the placenta. Abnormal blood rheology has been found in both preeclampsia and IUGR (Inglis *et al.*, 1982; Buchan, 1982; Hobbs *et al.*, 1982; Thorburn *et al.*, 1982). Lang *et al* (1984) showed that blood viscosity was increased at high shear rate, due in part to high haematocrit. Blood viscosity was also increased at low shear rate. Some studies (Thorburn *et al.*, 1982) have found reduced red cell deformability when filtration of cells was performed in native plasma but not in donor plasma. This would imply that a plasma factor may be responsible (Inglis *et al.*, 1982). Whole blood viscosity (ie. red cells in native plasma) at high shear was still elevated after correction to standard haematocrit (Lang *et al.*, 1984). This suggests that red cells are less deformable in preeclampsia, since high shear viscosity is influenced by red cell deformation under high shear conditions. Therefore, the consensus of opinion is that blood viscosity is increased and red cell deformability in native plasma is decreased in preeclampsia (Thorburn *et al.*, 1982; Lang *et al.*, 1984).

As regards tests of haemostasis, the levels of Factor VIII coagulant activity and antigen were increased in pregnancy hypertension (Lang *et al.*, 1984), although the ratio of activity to antigen was not altered. Hypofibrinogenaemia has been noted in severe preeclampsia (Birmingham Eclampsia Study Group, 1971). There is also reduced fibrinolytic activity (Bonnar *et al.*, 1969; Birmingham Eclampsia Study Group, 1971), increasing the chance of fibrin deposits. Fibrin degradation products (FDP's) were found to be raised (Bonnar, McNicol and Douglas, 1971; Condie, 1976) with a reduction of platelet count. It is difficult to know whether these changes are primary or secondary to the disease process. Since activation of the coagulation system is a feature of preeclampsia, changes in the levels of these substances is no great surprise.

Platelet activity

Platelet studies in normal pregnancy have yielded conflicting results, Giles *et al* (1981) reported no alteration in platelet numbers or Mean Platelet Volume (MPV) in 1087 normal pregnant women compared to non-pregnant controls. Harrison, Bramich and Collins (1982) also found no change in the platelet count in normal pregnancy. In contrast, Hsieh and Cauchi (1983) reported a fall in MPV in normal pregnancy, most profound in the first trimester but sustained throughout normal pregnancy. Fay, Hughes and Farron (1983) have reported a significant drop in platelet numbers in the last 8 weeks associated with a rise in the MPV in the last four weeks of normal gestation, and Still, Lind and Walker (1985) have recently reported increased MPV and Platelet Distribution Width (PDW) between 34 and 37 weeks. Many studies in women with pregnancy induced hypertension and preeclampsia have reported changes in platelet numbers, platelet survival and MPV which have been interpreted as evidence of increased platelet consumption (Redman, Bonnar and Beilin, 1978; Wallenburg and Rotmans, 1980; Giles, 1981; Hsieh and Cauchi, 1983). Thrombocytopenia is a common finding (Birmingham Eclampsia Study Group, 1971), is associated with progressive disease (Redman, Bonnar and Beilin, 1978; Trudinger, 1976) and has been shown to be related to disease severity (Howie, Prentice and McNicol, 1971). Platelet life span is known to be reduced in PIH (Rakoczi *et al.*, 1979) and this is thought to be secondary to intravascular platelet aggregation and increased adhesion to damaged vascular endothelium. If platelets are activated, betathromboglobulin (BTG) and serotonin are often increased in the plasma. Increased betathromboglobulin has been found (Douglas *et al.*, 1982; Socol *et al.*, 1985) but Lang (1984) found no increase. Serotonin levels have been found to be raised (Jelen, Fananapazir and Crawford, 1979) in pregnancy induced hypertension and intraplatelet serotonin levels are decreased (Whigham *et al.*, 1978). Page (1972) suggested that there is varying activation of the coagulation system and platelet aggregation but the trigger to this activity is unknown. It is also not known whether this is a primary or secondary effect. The differences seen may be related to differing disease severities in the study groups.

The relevance of Oedema

As already discussed oedema is found in 85% of women with preeclampsia (Thomson, Hytten and Billewicz, 1967) and may be severe. The oedema fluid is an ultra-filtrate of plasma and is associated with reduced plasma albumin and osmotic pressure, and with retention of sodium and potassium. However, it has little value as a specific diagnostic sign as oedema occurs in 64% of normal pregnancies (Thomson, Hytten and Billewicz, 1967; Dexter and Weiss, 1941) and is associated with no increase in perinatal mortality (Thomson, Hytten and Billewicz, 1967; Chamberlain

et al., 1978b). Although Hamlin (1952) found that all patients who developed PIH had been noted to show oedema during the preceding 6 weeks, others have found that patients with oedema had an incidence of PIH which was similar to patients without oedema (MacGillivray and Campbell, 1980). In fact, retention of fluid is associated with heavier babies (Duffus *et al.*, 1969). There are other signs of loss of intravascular volume. Haemoconcentration also occurs (Zangemeister, 1903). Dieckmann in his monograph "Toxaemias of Pregnancy" (1952) states that serum protein concentration rises at least two days prior to the development of eclampsia as does the haematocrit and haemoglobin. This demonstrates the association of the hypertension with a reduced plasma volume (Gallery, Hunyor and Gyory, 1979). There is controversy over whether the cardiac output is increased, unchanged or reduced (Werko, 1950; Assali and Vaughn, 1977; Rafferty and Berkowitz, 1980). Most studies have been done on patients where various treatment regimes have already been instigated and this may explain the differences found.

Proteinuria

As already discussed, proteinuria in pregnancy induced hypertension is related to disease severity (MacGillivray, 1961; Nelson, 1955b). The proteinuria is moderately selective in terms of size of the filtered proteins, but can be heavy with more than 5 grams of protein per day being lost. It is due to a glomerular protein leak, signifying glomerular involvement in the disease process. As this is always associated with the pathognomonic renal lesion, this will be discussed under renal pathology.

Convulsions and coma

Severe hypertension causes arterial damage and this has been demonstrated in animals (Goldby and Beilin, 1972). This arterial damage may explain the convulsions and cerebral haemorrhage seen in untreated severe preeclampsia . Cerebral haemorrhage is the commonest cause of death in pregnancy induced hypertension (DHSS, 1969; DHSS, 1974; DHSS, 1979; Turnbull, 1987; Turnbull *et al.*, 1989). Postmortem studies of the brain show oedema, hyperaemia, focal lesions, thrombosis and haemorrhage (Sheehan and Lynch, 1973; Smorl and Veit, 1933). As these lesions were found at postmortem, they may be end stage changes rather than causal lesions. The length of time after death that the studies were carried out also may contribute. Sheehan (1950) studied 48 cases within one hour of death. Haemorrhages were the most common findings. There was little oedema at this time. Govan (1961) showed that the cause of death in 39 of 110 women who died of PIH was cerebral haemorrhage. In a further 47 it was cardiorespiratory failure with small haemorrhages found in 85% of them. Fibrinoid changes were regular findings in the walls of the cerebral vessels. Because of the lymphocyte reactions around the lesions with infiltration by pigmented macrophages, they appeared to have been present for

some time. This could suggest that these lesions antedate the fit and are not caused by the seizure itself. Whether these lesions are the cause of the neurological symptoms and the fits is more difficult to discover. The relevant factor concerning whether a patient does or does not convulse, appears to be her own fitting threshold (Nelson, 1955b). The degree of pathological damage found may well be related to the amount of prodromal preeclampsia. Only some of the pathological signs may result from the damage due to the seizure itself.

Hepatic lesions.

The most characteristic feature of the hepatic lesion in eclampsia is its variability in extent and severity. Many cases are described with no hepatic necrosis at all (Acosta Sison, 1931; Bell, Dieckmann and Eastmann, 1940; Theobald, 1933). The changes seen within the liver are not related to severity, although the pathological damage can be quite extensive (Sheehan and Lynch, 1973; Dieckmann, 1929). Therefore, it is thought that the lesions are caused by the condition and do not contribute to the aetiology of the disease. In biopsies of five patients who survived eclampsia, a normal liver was found in two. In a further two patients, the lesions were found to be worse than those found in the patients who died (Ingerslev and Teilum, 1946). The hepatic findings are mostly related to end stage disease and are found at postmortem. Because most of the early studies were carried out on patients who had died, this led to the opinion held in the 1930's that haemorrhagic necrosis in the periphery of the lobules is the characteristic lesion of eclampsia (Acosta Sison, 1931).

The lesions are most commonly found in the right lobe of the liver. The areas of haemorrhage begin around a periportal space and are usually associated with extensive thrombosis in the smallest vessels in the periportal connective tissue. Sheehan and Lynch (1973) thought that the primary lesion was the escape of blood or plasma into the peripheral base of the hepatic cell cords. Focal fibrosis is usually seen. Lesions of the centre of the hepatic lobule are also seen (Acosta Sison, 1931). Haemorrhage beneath the liver capsule may be so extensive as to cause rupture of the capsule with massive haemorrhage into the peritoneal cavity (Golan and White, 1979). Therefore, hepatic lesions are patient specific rather than related directly to disease severity.

Renal Lesions

In normal pregnancy there is an increase in the glomerular filtration rate (GFR) of 50%. This leads to a reduction in the plasma urea and creatinine concentrations.

In preeclampsia there is a reduction in the GFR leading to a rise in plasma creatinine and urea and a fall in the creatinine clearance rate. In severe preeclampsia there is a characteristic increase in the amount of protein excreted by the kidney into the

measurable range (above 300 µg/l). In the presence of proteinuria, renal lesions are usually found (Sheehan, 1980; McCartney, 1964)

Altchek, Albright and Sommers (1968) showed that the typical biopsy lesions are:-

1) Glomerular Lesions.
2) Juxtaglomerular cellular hyperplasia.
3) Lesions of the loop of Henle.
4) Afferent arteriolar spasm.

Glomeruli are enlarged by 20% with cellular swelling and glomerular capillary endotheliosis (Fig. 3.2). All glomeruli appeared affected but the distribution within the glomeruli was patchy. There was an increase of the number of cells and thickening of the capillary endothelium between the capillaries explaining the appearance of the splitting of the basement membrane seen by light microscopy. This is really an increase in the mesangial matrix. Capillary endothelial cells were swollen and many lumina appeared empty or absent. Deposition of fibrin protein strands were seen within Bowmans capsule. Vassalli, Morris and McClusky (1963) have found fibrinogen within these lesions. Immunofluorescent studies suggested that the deposits seen on the basement membrane are fibrinogen derivatives. This supports the view that preeclampsia is an upset of the coagulation system. The epithelium of Henle's loop was severely desquamated with fragments of nuclei and cells evident. In other areas regeneration was apparent. Afferent arterioles showed marked vasospasm.

Tubular lesions are also common and casts are seen in the urine. Chesley (1971) showed that the kidney has a decreased ability to secrete uric acid in preeclampsia, hence the increase in the concentration of uric acid and a fall in bicarbonate concentration. Uric acid is filtered completely by glomeruli, reabsorbed completely by proximal tubules and then secreted by distal convoluted tubules. Therefore, in preeclampsia, the initial filtering may be reduced by glomerular impairment or the secretion may be deficient due to tubular damage. In support of the latter possibility, Altchek, Albright and Sommers (1968) have reported a lesion in the Loop of Henle, the severity of which is related to the level of uric acid. They and Pollak and Nettles (1960) have shown hyperplasia of the juxtaglomerular apparatus (JGA) and apparent cellular hyperactivity. The JGA was swollen with an increase in the number of cells and vacuolation. There is an increase in renin, angiotensin and aldosterone activity. This could lead to retention of sodium and water. However these lesions appear to be progressive with the disease and may be secondary to the volume depletion rather than being an aetiological factor. Dieckmann (1952) has reported the rare lesion of cortical necrosis which was fatal although it can now be managed by renal dialysis. The lesion is caused by spasm of the renal arteries and anaemic infarcts. This lesion is not specific to pregnancy.

After delivery the changes disappear with occasional traces of increased mesangial matrix. Petrucco *et al* (1974) did not see the changes of the JGA or the Loop of Henle but their samples were taken from the recovery phase post delivery while the findings of Altchek's (1961; 1964; 1968) and other's came from renal biopsies taken during the active phase. Sheehan showed that the renal changes regress quickly after delivery (Sheehan, 1950).

These findings were summarised by Zuspan (1978) as :-

1) Disease of arterioles.
2) Increased vascular sensitivity and reactivity.
3) Sodium retention.
4) Decreased glomerular filtration rate.
5) Decreased intravascular compartment.
6) Increased irritability of the central nervous system.
7) Negative nitrogen balance.

Placental lesions

The fetus depends on the placenta for its survival. The ability of the placenta to exchange nutrients and gases with the fetus is largely dependent on blood flow, both in the mother and in the fetus. It has been known for some years that the blood flow to the placenta is reduced in maternal hypertension (Browne and Veall, 1953; Dixon and Robertson, 1958; Assali *et al.*, 1954). More recently, Campbell (1983) has show abnormalities in the uterine artery velocity wave form as early as 18 weeks in patients who are destined to develop preeclampsia and IUGR.

These observations might be explained by the pathology in the terminal segments of the uterine spiral arteries. Within the placenta, these become obstructed by fibrin and platelet aggregates. Placental infarcts are also seen. However, these 'so-called' infarcts are found in about 60 per cent of normal pregnancies. Tenney and Parker (1940) believe that the characteristic placental change is one of premature aging. Fox (1978) disregards this term and calls the lesions ischaemic villus necrosis. Tenney and Parker (1940) found that in preeclampsia most of the villi show syncytial degeneration, a finding in only 10 to 50% of normal pregnancy. Extensive infarcts of more than 5% of the placental area are not found in normal pregnancy (Fox, 1978) but are found in increasing frequency in patients with worsening hypertension. This lesion is not specific to preeclampsia and occurs in essential hypertension without evidence of superimposed preeclampsia. It is likely that these changes are those of hypertensive damage of whatever cause (Fox, 1978). The work of Dixon & Robertson (1958), Brosens *et al* (1970; 1977), Robertson and Dixon (1967) and Robertson (1976) showed the obvious differences between normal and preeclamptic pregnancies (Fig. 3.6). The fundamental lesions are in the spiral arteries of the placental bed. There is a failure of the normal invasion of the maternal spiral arteries by the trophoblastic cells. This invasion is necessary to destroy the musculo-elastic tissue in the media to

allow vasodilatation of the spiral arteries. There is then failure of the normal vasodilatation of these arteries leading to a reduced placental blood flow. The trigger for failure of the normal physiological changes in the maternal blood vessels is unknown but could be due to immunological reaction similar to graft rejection. An immune aetiology has been previously discussed. More recent studies by Sheppard and Bonnar (1981) suggest that these lesions are not specific to preeclampsia but are found in the vessels from pregnancies with intrauterine growth retardation, with or without hypertension.

These placental changes give rise to interference with fetal growth and oxygenation. Bastiaanse and Mastboom (1950) claimed that uteroplacental ischaemia was responsible for preeclampsia. Therefore, the maternal changes seen in pregnancy induced hypertension may be secondary to placental ischaemia. Animal models of the disease depend on procedures which cause placental ischaemia (Cavanagh *et al.*, 1977). This theory would support Symonds belief that uteroplacental stimulation of the renin/angiotensin system secondary to placental ischaemia plays a central role in the development of hypertension (Symonds, 1981).

Hereditary factors

There is increasing evidence that severe preeclampsia is a familial disease (Adams and Finlayson, 1961; Chesley, Annitto and Cosgrove, 1968; Cooper and Liston, 1979). Chesley, Annitto and Cosgrove (1986) traced 96% of the grown daughters of the women who had had eclampsia at the Margaret Hague Maternity Hospital. The incidence of preeclampsia in daughters was 26%. It was 32% in sisters and 16% in granddaughters. Adams and Finlayson in a study of sisters found a strong family association. Humphries (1960) looked at the mothers of women who had eclampsia in the Johns Hopkins Hospital in Baltimore. There was an incidence of 28% in the mothers compared with 13% in other random patients. Sutherland *et al* (1981) studied the mothers and mothers-in-law of patients with severe preeclampsia. The study showed that mothers-in-law did not have an incidence higher than expected (4%) but mothers did (14%). So the condition appears to be passed from mother to daughter and is not transmitted by the husband. Therefore, a single recessive gene in the mother and not the fetus could be responsible for the development of pregnancy induced hypertension (Cooper and Liston, 1979). This is unlikely to be true as other factors are undoubtedly involved. It is more likely that the hereditary factors are dominant in nature with only 50% penetrance. This would allow for the other factors to influence the disease penetration and reduce the incidence of the carrier gene required in the population to support the single recessive gene theory. Incomplete penetrance is very difficult to distinguish from multifactorial inheritance.

Similar inherited tendencies are not found in mild preeclampsia or late onset disease. This implies that this condition may have a different aetiology, that it represents a mixed group or that it is the adaption to the disease process that is related to inheritance.

Miscellaneous factors

The condition is thought to be more frequent in the obese (Oats *et al.*, 1983) and it appears to be related to the weight at the start of pregnancy (Peckham and Christianson, 1971). However, fat women have higher blood pressure and it is difficult to measure as the arm is too big for a normal sphygmomanometer cuff.

There are no differences in the incidence of preeclampsia in the different social classes (Duffus and MacGillivray, 1968) except for a slight increase found in social class III. Women who smoke have a lower incidence of disease (Duffus and MacGillivray, 1968) but if preeclampsia develops, it tends be of a more severe form than average. Although it has been advocated that eclampsia was partly due to dietary deficiencies (MacGillivray and Johnstone, 1978), there is little evidence for this. Brewer (1969) agreed but based his argument on the fact that the incidence of preeclampsia was higher in underprivileged black groups. This difference found in social groups is not universal (Duffus and MacGillivray, 1968) and some of the changes may be racial rather than social. Others found that diet has no effect on the incidence but may affect outcome (MacGillivray, 1981).

Discussion

Much of what has been described are epiphenomena that relate to each other. They are not in themselves causes of preeclampsia. There are however two basic abnormalities that are persistently found.

1) Abnormalities of **placentation**, evidence of which can be found early in pregnancy before the clinical manifestations of the disease are apparent. Preeclampsia is also associated with excessive placentation, as in twin and molar pregnancies.
2) Abnormalities of **platelet/vessel wall interaction**, leading to increased vascular sensitivity and platelet consumption. The vascular activity also appears to antedate the clinical signs of preeclampsia. These changes may be mediated through the prostaglandin system.

As already stated there appears to be no difference between the placental changes found in preeclampsia and IUGR. The reason that some patients present with high blood pressure probably depends on their vascular reactivity (Fig. 3.7). The risk of convulsion appears to be related to the patient's seizure threshold as it is not directly related to the blood pressure alone.

It is obvious that patients may carry the susceptibility to vascular reactivity, as described by Wallenburg (1986), without developing preeclampsia. What is required is

a further trigger which would come from the placenta. This stimulus may be mediated through the renin/angiotensin system but this is liable to be a messenger rather that a cause. The stimulus would be produced either from the ischaemic, small, poorly implanted placenta of classic preeclampsia or from a large placenta found in a multiple pregnancy. The vascular reactivity is also associated with other vessel wall functional abnormalities such as increased platelet activation.

Most of the other signs found in this condition could be explained from these two main "primary" problems.

This does not explain why these events occur.

There is strong evidence that there is an **immunological** role in preeclampsia.The immunological influence is most likely to be involved in the initial implantation abnormalities leading to the spiral artery pathology related to placental insufficiency.

There is also strong evidence of an **hereditary** role. This could be involved in the vascular sensitivity seen by Gant and Wallenburg. If this was true, it could not be an autosomal recessive disorder but is more likely to be an autosomal dominant with incomplete, around 50%, penetrance. This would fit the results described by Wallenburg (1986) (Fig 3.5)

3.3 The risks of pregnancy hypertension

Hypertension in pregnancy is not a disease in itself but a reflection of a maternal response to an underlying disease. It can however be used as a marker of risk for the mother or the baby. The risks associated with any measurement can be used in the assessment of whether that measurement is abnormal or not. Since preeclampsia is a multisystem disorder, blood pressure alone may be inadequate for assessing absolute risk. The disease affects different organs in different ways and to different degrees. The risks to the mother and baby depend on how the disease affects the patient and which organs are involved. Not all patients with the same abnormalities of disease parameters will necessarily have the same risks. The problems for the mother and the baby are different and they will be treated separately.

Risks to the mother

In modern obstetric practice, hypertension in pregnancy produces a management dilemma. The risks to the mother are difficult to assess.. The figures from the Scottish maternal mortality report show that the vast majority of the patients do well (1987). The risk of maternal death associated with hypertension is only 1:11000 which is not much different from the rate for pregnancy as a whole. However, the recent confidential inquiries into maternal deaths in England and Wales, have shown that hypertension in pregnancy remains the biggest killer of pregnant women. 20.5% of maternal deaths are associated with pregnancy induced

hypertension and another 8.3% related to other hypertensive related factors (Turnbull *et al.*, 1989). A look at the rates over the last four reports show that there has been little change over the last 20 years (Table 3.10) (Turnbull, 1987). The figures for Scotland are less clear as the numbers are smaller. PIH is the second biggest killer with pulmonary thromboembolism (PTE) first (Scottish Home And Health Department, 1989). If the cause of death within the hypertensive group is studied it can be seen that the main cause of death was cerebral haemorrhage and other types of cerebral damage (Table 3.11). The more traditional causes of mortality, such as renal failure, are now less common, partly due to improved medical support available. Even if patients with eclampsia are studied, cerebral haemorrhage still appears to be the main cause of mortality. The risk to both mother and baby appears to relate to the degree of preeclampsia preceding the seizure, rather than the seizure itself. Therefore, in the United Kingdom, although eclampsia is the main preoccupation of therapeutic approach, CVA is the main maternal risk of hypertension in pregnancy. As already stated, the level and the degree of the rise of the blood pressure correlates more closely to the risk of CVA than the risk of eclampsia. In most studies, about 30% of the patients who suffered seizures, had diastolic blood pressures of less than 90 mmHg. The chances of eclampsia occurring may be more related to the patient's seizure threshold than to the level of blood pressure (Nelson, 1955a). The risk of vascular damage with hypertension correlates with the animal studies that showed vessels are damaged when the diastolic blood pressure rises above 110 mmHg (Goldby and Beilin, 1972). Therefore, the main risks to the mother would appear to occur only after the blood pressure has reached 110 mmHg diastolic. Although convulsions may occur below this level, the maternal mortality and morbidity appear to be related to the vascular damage associated with the hypertension, rather than to the convulsions unless repeated convulsions occur. There are many cases in the literature showing that patients still die with enough anticonvulsants 'on board' to stabilise the seizures.

Because of the dramatic presentation, it was eclampsia that was recognised before the hypertension (Chesley, 1980). Even with modern methods of blood pressure measurement, it is often eclampsia that brings the patient to the attention of medical care. This is particularly true in the third world where there is less antenatal care available. This has lead to a preoccupation with the prevention and treatment of eclampsia. The risk of seizures in a hypertensive patient is greatly overrated. However there is little good evidence of the true risk. In the Johns Hopkins Hospital in the 1930's, less than 1 in 300 preeclamptics became eclamptic (Chesley, 1971). There were similar figures from Guys hospital at the same time (Gibberd, 1928). In Scotland, the incidence of eclampsia is 1 in 300 of the total of the

preeclamptic/eclamptic patients (Scottish Home And Health Department, 1989). Since many of the eclamptics show acute onset or are intrapartum/post partum patients with no prodromal preeclampsia, the incidence of eclampsia occurring in any hypertensive patient must be even lower than 1/300. **Therefore the risk of eclampsia for the average hypertensive patient is low, and the main risks of mortality is from the hypertension itself leading to CVA.**

A common belief is that delivery cures the patient with preeclampsia. If the Scottish figures are reviewed, it can be seen that all the patients that died, did so after delivery (Scottish Home And Health Department, 1989). Therefore, although the removal of the trophoblast will eventually remove the stimulus to the disease, this is not immediate and continued vigilance is required after delivery.

Delivery in the unstable patient is probably more dangerous than a delay in order to stabilise the situation. Intubation causes a further rise in BP of between 20 and 30 mmHg in both systolic and diastolic (Lavies *et al.*, 1989; Ramanathan *et al.*, 1988). This is associated with CVA's occurring under anaesthetic leading to postpartum death. Adequate therapy with antihypertensives and/or narcotics prior to intubation reduces this risk (Ramanathan *et al.*, 1988). Pulmonary edema is the next major cause of maternal mortality. This is often due to fluid overload partly caused by overenthusiastic replacement. Plasma protein solutions are particularly dangerous (Duncan, 1989). Although there may be depletion of the plasma volume, the vascular tree is contracted, reducing the capacity for fluid replacement. Some workers suggest that Swan-Ganz catheters are required to monitor the fluid replacement in order to reduce this iatrogenic cause of maternal mortality and morbidity (Wasserstrum and Cotton, 1986). The classical risks of renal and liver damage are rarely seen in present day practice in the United Kingdom, although they are still encountered in other parts of the world.

The reason for the reduction in renal risk is partly due to the availability of renal dialysis. but with adequate attention to the fluid balance and the careful monitoring of the urine output, renal failure should not occur. Coagulation abnormalities associated with elevated liver enzymes and haemolysis have recently been described and termed the HELLP syndrome (Weinstein, 1982). This may not be anything new as low platelets, liver problems and haemolysis are well recognised complications of preeclampsia (Pritchard, Cunningham and Mason, 1976). The realisation that these signs highlight a high risk patient is important however, as the assessment of risk in preeclampsia has often been arbitrary in the past.

Despite these well accepted risks to the mother, it should be remembered that the vast majority of these patients do well with little or no morbidity.

Risks to the fetus and neonate

The effects of hypertension on the fetus depend on the degree of involvement of the placenta, acute occurrences such as abruption, and the gestation at delivery (Scottish Home And Health Department, 1989).

Although preeclampsia is thought by many to be a placental disease (Robertson, Brosens and Dixon, 1967), it is plain that not all the pregnancies are equally badly affected. The incidence of intrauterine growth retardation is not absolute and many babies are well grown with no apparent placental insufficiency (Nelson, 1955b).

The classic pathology seen with preeclampsia consists of two parts. First there is the failure of the spiral arteries to dilate and lose their muscular coat and then there are secondary changes of infarction and thrombosis (Robertson, Brosens and Dixon, 1967; Fox, 1978). The first changes are probably present in most, if not all of the true preeclamptic patients, but the secondary changes are not universal and may not be present in all parts of the placenta in the same patient. It is the secondary changes that therapies, such as low dose aspirin, may prevent, thus reducing the effects of the disease. Many workers believe that it is the placental damage that leads to ischaemia. Such damage stimulates the release of vasoactive substances such as angiotensin II. These, in turn, produce the vasoconstriction and hypertension found in preeclampsia (Symonds and Broughton Pipkin, 1978). The secondary changes are similar in essential hypertension and may be partly an effect of hypertension. The primary changes in the spiral arteries are absent in essential hypertension but IUGR is associated with this form of disease.

Therefore, the effect on the baby depends not only on the presence of the disease but the degree of placental involvement. Although diastolic blood pressure above 95 mmHg is associated with an increased perinatal mortality (Friedman and Neff, 1975), the level of blood pressure does not appear to be a good marker in clinical practice. The Scottish Perinatal mortality statistics show that the percentage of the perinatal mortality rate associated with preeclampsia is around 18% (Scottish Home And Health Department, 1989). The percentage associated with severe disease is 5% and 13% are associated with mild disease. This implies that the overall risk of perinatal death in the patient with preeclampsia is less than the overall perinatal mortality rate. This is still true for patients with severe disease (Table 3.12).

So, if blood pressure does not necessarily help in the prediction of perinatal outcome, is there anything that is better. Redman (1976) showed that uric acid was a better predictor of poor perinatal outcome than blood pressure. The increasing uric acid level is thought to be a sign of the renal involvement in the disease. The platelet count also falls in patients with progressive disease before the increasing severity becomes apparent (Redman, Bonnar and Beilin, 1978). Platelet consumption is

thought to be associated with placental deposition and fibrin formation (Robertson, Brosens and Dixon, 1967). This could be a sign of impending placental insufficiency. There is a higher incidence of IUGR in cases of perinatal mortality associated with hypertension compared to the other causes of perinatal mortality (Scottish Home And Health Department, 1978; Scottish Home And Health Department, 1987; Scottish Home And Health Department, 1989).

Therefore the risks to the fetus are associated with changes found in placental insufficiency.

In the presence of a normally functioning placenta, is hypertension any problem to the fetus at all? If the hypertension remains mild or moderate, the risk to the fetus appears to be less than normal (Nelson, 1955a).

In cases of eclampsia, the risk to the fetus relates to the degree of preeclampsia that existed prior to the convulsion rather than the convulsion itself.

There is a small increase in the incidence of abruption (Chamberlain *et al.*, 1978a), but the risk only appears to rise when the systolic blood pressures is above 200 mmHg (Dunlop, 1966).

One of the significant causes of perinatal mortality in pregnancies complicated by pregnancy hypertension is prematurity. Many workers have shown the poor outcome of hypertensive pregnancies in the second and early third trimesters (Sibai *et al.*, 1985). Some have suggested that it is a different disease (Moore and Redman, 1983).

The reason for this is obvious. If the patient has severe disease in the early gestations, delivery of the fetus carries a poor outcome whereas severe preeclampsia occurring at 34 weeks can easily be treated by delivery with an excellent prospect of a satisfactory fetal outcome. In later pregnancy, the presence of placental insufficiency increases the risk of fetal mortality and morbidity irrespective of the degree of blood pressure rise.

Therefore, the need to deliver the baby in the maternal interest is only a risk to the fetus in the earlier trimesters when, despite good growth and wellbeing, the fetus may well die because of prematurity. The other risk is of placental insufficiency and IUGR which can cause problems at any gestation and with any severity of hypertension. This can be seen in the Scottish perinatal mortality figures which show that the perinatal loss associated with PIH is mostly postnatal prior to 32 weeks and antenatal after 32 weeks (Scottish Home And Health Department, 1989)

As the risk to the fetus varies with gestation, in order to reduce this loss, a two pronged approach is required; attempt to prolong the pregnancies to allow improved fetal viability in the early gestations; and increase fetal monitoring to reduce intrauterine death in the later pregnancies.

3.4 The Management Of Hypertension In Pregnancy

Historical Perspective

Eclampsia was the first presentation of this disease that was recognised (Chesley, 1980). It is not surprising that the treatment was directed at this symptom of the disease (Stroganoff and Davidovitch, 1937). Even today, when the whole spectrum of the disease is known, the mainstay of most protocols is anticonvulsant therapy (Menon, 1961; Zuspan, 1966; Pritchard and Pritchard, 1975; Sibai *et al.*, 1981a). This is despite the fact that more mothers die without convulsion than die following convulsion (Turnbull, 1987). It was also realised that delivery was the definitive treatment as the condition only occurs in the presence of a placenta and resolves after removal of the placenta (Chesley, 1980). Therefore, most therapeutic regimes were based on sedating of the mother and expediting deliver of the fetus.

Methods of therapy in hypertension of pregnancy

Prevention would be the best form of treatment, but as we do not know the cause we therefore do not know how to prevent this condition. Early studies of manipulation of the prostaglandin/thromboxane balance look encouraging, but the results of the CLASP (Collaborative Low dose Aspirin Study for the Prevention of preeclampsia and growth retardation) study controlled from Oxford and the large American study are awaited. Early detection of the condition would help provide an opportunity for early treatment that might alleviate the worst effects of the condition. Various tests such as the cold pressor test, the flicker fusion test and the roll over test have been tried to detect the very early changes of preeclampsia, but they have not been found to be of practical value. However, even if early detection is achieved, what are the therapeutic options?

Hospitalisation and bed rest

If the blood pressure is found to be raised to a diastolic pressure of over 90 mmHg or if there is protein in more than trace amounts in a midstream specimen of urine, most obstetricians felt that the patient should be admitted to hospital (Hamlin, 1952; Chamberlain *et al.*, 1978a; Cunningham and Pritchard, 1984). Bed rest is probably one of the most widely used methods of treating this condition, although no randomised study has proven its value (Matthews, 1977a; Crowther and Chalmers, 1989). If the blood pressure remained just below 90 mmHg or fell below 90 mmHg on resting, the patient would then be allowed to rest at home. Sedation was often prescribed, e.g. Sodium Amytal, 200 mg or Diazepam (Valium) 5 mg (Chamberlain *et al.*, 1978a). It has been shown that bed rest increases the placental blood flow but it is not known whether this is necessarily beneficial. It also reduces the venous pressure in the lower extremities and allows a reabsorption of a considerable amount of the oedema. This can give a false impression that the condition is improving.

Matthews, in a randomised trial, showed that management at home was as good as hospitalisation in nonproteinuric preeclamptic patients (Matthews, 1977b). There appeared to be no need to admit to hospital. If patients are admitted, the blood pressure is often found to be normal and more than half the patients admitted with hypertension were found to be wrongly diagnosed (Hall, Chang and MacGillivray, 1980).

If the blood pressure remained up and particularly if proteinuria was present the patient would normally stay in hospital. She may be allowed up to the toilet but otherwise bed rest would be complete. Sedation was often increased (Chamberlain *et al.*, 1978a).

Salt restriction and Diet

Since a patient with preeclampsia has salt and water retention, salt restriction and the use of diuretics might initially appear attractive. However, changes in dietary salt have no effect on the clinical course of preeclamptic patients (MacGillivray, 1981).

Low calorie diets have been tried in an attempt to prevent or to treat preeclampsia, but a controlled trial has shown that there is no difference in the incidence of proteinuric preeclampsia in primigravidae given a low calorie diet compared with matched controls, although the weight of the babies was reduced (Campbell and MacGillivray, 1975). Therefore, diets do not appear to reduce the incidence of preeclampsia or improve the condition once it is established.

Sedation

Magnesium sulphate was popular as part of the Stroganoff treatment which originated from Russia in the early part of the century (Stroganoff and Davidovitch, 1937) and its use has continued mainly in North America, in the treatment of eclamptic convulsions or as a sedative in the severe form of preconvulsive state. Large doses of magnesium sulphate may produce depression of the vital centres. The margin of safety is small but it remains the regime of choice in eclampsia and severe preeclampsia in the USA (Pritchard and Pritchard, 1975; Sibai, Graham and McCubbin, 1984; Lee, Todd and Bowe, 1984; Zuspan, 1966; Dinsdale, 1988). Even there, it is not universally accepted (Kaplan *et al.*, 1988; Dinsdale, 1988; Donaldson, 1988).

Many other methods of sedation have been used. The so-called 'Lytic cocktail' was composed of 25 mg of chlorpromazine, 100 mg of pethidine and 50 mg of promethazine. It was extensively used in the treatment of eclampsia by Menon (1961) in Madras. Although a good anticonvulsant, it could cause respiratory depression in the babies.

Morphia has been used in the treatment of fulminating preeclampsia and eclampsia.

Amylobarbitone sodium (Sodium Amytal) was given in a dose of 200 mg nightly or four- to six-hourly depending on the severity of the condition (Chamberlain *et al.*, 1978a). Paraldehyde was popular in some places but it was usually given rectally and was not a very efficient anticonvulsant. Diazepam (Valium) is an efficient anticonvulsant and it is still widely used. It has some hypotensive effect but overdosage is relatively easy and respiratory depression may be encountered particularly if given in conjunction with barbiturates.

Chlormethiazole (Heminevrin) given by continuous intravenous infusion is a commonly used anticonvulsant. The perinatal mortality with chlormethiazole was only half that found with bromethol or paraldehyde (Duffus *et al.*, 1969).

The use of antihypertensive drugs in pregnancy.

Antihypertensive drugs reduce blood pressure. The pharmacological action of many of these drugs is still not fully understood. They may act in different ways but the results of the action are the same. All antihypertensive drugs have side-effects, some of which may produce further benefits and others harmful results (De Sweit, 1985; Lubbe, 1984). Since they are powerful cardiovascular agents, it would be surprising if they did not have some adverse fetal effect (Schoenfeld *et al.*, 1989). The obstetrician must balance any potential benefit of antihypertensive therapy against any potential side-effect that might occur. There is no consensus about therapy for pregnancy hypertension and the role of antihypertensive drugs (Lubbe, 1984; Rubin, 1981; Chamberlain *et al.*, 1978a; Trudinger and Parik, 1982).

Which drugs are available?

Drugs exist that can alter the responses of every known blood pressure control system. They can be divided into five main groups:- centrally acting drugs, drugs that alter cardiac output, drugs that effect the peripheral vascular resistance, angiotensin converting enzyme inhibitors and diuretics.

Centrally acting drugs

The main centrally acting drugs are methyldopa and clonidine. They act by central inhibition of the sympathetic drive (Frolich, 1980; Houston, 1981). All drugs that act in this way are associated with troublesome side effects and have led to the move away from these products in the non-pregnant patient (Reid and Elliot, 1984). Clonidine, an alpha-adrenoceptor agonist, has been used successfully in pregnancy to control blood pressure, but the experience is limited (Horvath *et al.*, 1985).

Methyl dopa

Methyl dopa is still the most widely used drug for pregnancy hypertension throughout the world. This is partly due to its relative inexpensiveness but also its apparent safety (Leather *et al.*, 1968; Redman *et al.*, 1976). Its mode of action is not fully understood. Oral absorption is poor with oral bioavailability of less than 30%.

An oral dose of 250-1000 mg will reduce blood pressure within 2-3 hours, with a peak effect at 4-8 hours and lasting 10-12 hours. There is a small degree of bradycardia but little or no alteration in cardiac output. The hypotensive effect appears to be related to a reduction in the peripheral resistance following a reduction in sympathetic drive. The use of methyl dopa is associated with a relatively high degree of maternal side effects. The most common are sedation, dry mouth, nasal congestion, depression and postural hypotension (Redman *et al.*, 1976).

Drugs that alter cardiac output

The mode of action of beta adrenoceptor blockers is not fully understood but the consistent haemodynamic feature of beta-adrenergic blockade is a reduction in the cardiac output (Lund Johansen, 1980). In the non-pregnant hypertensive patient, the cardiac output is often increased and the peripheral resistance is normal. Therefore, beta-blockers are well suited for the treatment of chronic hypertension.

Not all these drugs act in the same way. They can be subdivided into those that are blockers to both β1 and β2 receptors, selective β1 receptor blockers, those with intrinsic sympathomimetic activity (ISA), different lipid solubility and membrane stabilising effects. These different properties can alter both the beneficial and harmful effects of these drugs. Widely used in the non-pregnant patient, their initial use in pregnancy was associated with some degree of hesitation. They were thought to have depressant effects on the fetal circulation and uterine tone. In addition, studies had suggested that they might be associated with adverse effects such as neonatal hypoglycaemia (Haraldsson and Geven, 1989), neonatal hypotension, depression of fetal heart rate (Ingemarsson *et al.*, 1984), impairment of the stress response (Dagbjartsson *et al.*, 1985) and intrauterine death (Lieberman *et al.*, 1978). Most of these studies, however, have been anecdotal or stem from animal research rather than human experience (Dagbjartsson *et al.*, 1985). They have not been confirmed in prospective studies. Adrenoceptor antagonists are now widely used in the treatment of preeclampsia in Europe and Australia (Rubin, 1981; Dubois *et al.*, 1982; Pontonnier, 1984). They are widely accepted as being safe to use although those without intrinsic sympathomimetic activity may increase the chance of intrauterine growth retardation (Dubois *et al.*, 1982; Lardoux *et al.*, 1983b). The drugs that have been studied the most are the non-selective blockers pindolol (Kahhale *et al.*, 1985; Dubois *et al.*, 1982) and oxprenolol (Gallery *et al.*, 1979; Gallery, Ross and Gyory, 1985; Fidler *et al.*, 1983), the selective blockers atenolol (Rubin *et al.*, 1983; Lardoux *et al.*, 1983b; Dubois *et al.*, 1982) and metoprolol (Sandstrom *et al.*, 1983) and the combined alpha/beta blocker labetalol (Lardoux *et al.*, 1983b).

Labetalol

Labetalol is a unique adrenoceptor antagonist as it has both α1-adrenoceptor

antagonist and non-selective β-adrenoceptor antagonist properties. The β-blocking effect of labetalol is four times less potent than that of propranolol. It appears to produce its hypotensive effects without compromising the maternal cardiovascular system by producing peripheral vasodilation (Lund Johansen, 1984). This may help to maintain renal and uterine blood flow. The acute administration of labetalol causes a reduction in blood pressure, heart rate and peripheral resistance, but there is no change in the cardiac output in standing and supine positions (Lund Johansen, 1980).

Drugs that effect the peripheral vascular resistance

These drugs act on the vascular wall to reduce peripheral resistance. The main examples are among the oldest and the newest antihypertensive drugs.

Diazoxide

Diazoxide is a benzothiadiazine derivative that is closely related to the thiazide diuretics. It has no diuretic activity and has a direct action on the arteriolar smooth muscle (Koch Weser, 1976). In large doses it is associated with acute fetal distress and intrauterine death (Ayromlooi *et al.*, 1982). Small intermittent doses of 30 mg would appear to be safe and efficient in lowering blood pressure in the acute situation (MacLean *et al.*, 1981).

Hydrallazine

Hydrallazine is the oldest antihypertensive drug still in regular clinical use. It acts directly on the vascular wall requiring an intact endothelium to produce its effect and acts best with the patient lying flat in bed. Although its action is not fully understood, it may be mediated by prostaglandins. The fall in blood pressure results from vasodilation. Used as monotherapy, hydrallazine produces side-effects such as tachycardia, flushing, nasal congestion, tremors, headaches, nausea and vomiting (Koch Weser, 1974). A few subjects may be unusually sensitive to hydrallazine because of a reduced capacity to metabolise the drug. The use of hydrallazine is usually restricted to single or short term use. Prolonged use leads to both the stimulation of the renin-angiotensin-aldosterone system and the reduction in renal perfusion pressure. This can cause fluid retention with blunting of the drug's hypotensive effect and increasing the chances of cardiac failure. It is more effective in lowering diastolic blood pressure than systolic blood pressure. Acute administration is associated with reduced placental blood flow (Lipshitz, Ahokas and Reynolds, 1987) and fetal distress (Vink, Moodley and Philpott, 1980). The effect of a single dose of hydrallazine wears off in about 2/3 hours. Orally, the effect is minimal but can be used as an adjunct to beta-blocker therapy (Bott Kanner *et al.*, 1980).

Nitroprusside

Sodium nitroprusside is an effective intravenous drug for the management of acute

hypertension in the non-pregnant patient. It has been used in pregnancy but there is concern about the effects on the placental blood flow and the potential toxic effects (Shoemaker and Meyers, 1984; Stempel *et al.*, 1982). Because it is light sensitive, it is difficult to give. There are easier and as effective drugs which are preferable to use.

Calcium channel blockers

Calcium channel blockers act primarily by inhibiting extracellular calcium influx into cells through slow calcium channels. They reduce peripheral resistance and their action is proportional to the amount of vasoconstriction (Olivari, Bartorelli and Polese, 1979). They are antagonistic against any form of vasoconstrictor and have a mild tocolytic effect (Ulmsten, 1984). The drugs which are most used in primary hypertension are nifedipine, nicardipine and verapamil. They are potent orally and are used alone (Barton, Hiett and Conover, 1990; Seabe, Moodley and Becker, 1989; Walters and Redman, 1984) or in combination with β-adrenergic blockers (Constantine *et al.*, 1987).

They can be used in the acute situation or chronically. Animal studies have suggested that placental blood flow is reduced by nicardipine (Parisi, Salinas and Stockmar, 1989b) and there is an increase in fetal hypoxia (Parisi, Salinas and Stockmar, 1989a). Other studies do not support this (Ahokas *et al.*, 1988) and human experience suggests that with therapeutic dosage, calcium channel blockers are safe (Hanretty *et al.*, 1989; Lindow *et al.*, 1988).

Angiotensin converting enzyme (ACE) inhibitors

ACE inhibitors are relatively new, very effective drugs for treatment of hypertension in the non-pregnant patient. They act by inhibiting the action of the angiotensin converting enzyme. This reduces the production of angiotensin II and reduces peripheral vascular resistance (Cody *et al.*, 1978). There is no reflex tachycardia. This action may seem attractive for use in preeclampsia with its abnormalities of angiotensin II (Symonds, Broughton Pipkin and Craven, 1975). However, the original ACE inhibitor, captopril, has been found to have unacceptable side effects both in animal experiments and clinical practice (Broughton Pipkin, Turber and Symonds, 1980). Fetal deformity, neonatal renal failure, intrauterine death and a significant reduction in placental blood flow have all been reported. When captopril was given to pregnant sheep and rabbits, there was an appallingly high fetal and neonatal death rate in both species. It was concluded that this treatment should not be used in humans (Broughton Pipkin, Turber and Symonds, 1980). Enalapril is a newer drug with less side effects but adverse reports have begun to appear in the literature (Scott and Purohit, 1989). For these reasons their use in pregnancy must be restricted. However, they may be used in the postpartum period when blood pressure control is difficult to achieve.

Diuretics

The mechanism of action of diuretics is not definitely known but they probably act by a mild vasodilator action (Morgan, Mendelsohn and Doyle, 1980) and by reducing plasma volume by altering sodium balance (Winer, 1961). The thiazide diuretics are the most commonly used often in combination with other drugs (Finnerty *et al.*, 1979). Thiazides do not significantly lower the blood pressure in pregnancy (Gray, 1968; Kraus, Marchase and Yen, 1966) and have proved dangerous by induction of severe hyponatraemia (Pritchard and Whalley, 1961) and causing acute pancreatitis in the mother (Menzher and Prystowsky, 1967) and the fetus (Minkowitwitz *et al.*, 1964). A rise in blood urea and uric acid (Breckenridge, 1966), neonatal thrombocytopenia (Rodriguez, Leikin and Hiller, 1964) and hyperglycaemia and glycosuria in diabetic or prediabetic patients (Goldman *et al.*, 1969) can all be produced by the use of thiazide diuretics. There is some evidence to indicate that they can decrease placental function (Campbell and MacGillivray, 1975). A double blind study of the continuous prophylactic use of hydrochlorothiazide, 50 mg daily, in 1030 obstetrical patients demonstrated that there was no alteration in the incidence of preeclampsia, hypertension, prematurity, congenital anomalies or perinatal mortality (Kraus, Marchase and Yen, 1966). However, Collins reviewed the available literature and concluded that there was not enough evidence to prove that diuretics are dangerous (Collins, Yusuf and Peto, 1985) and Sibai (1983) showed that patients with chronic hypertension on diuretics can have the normal blood volume changes of pregnancy. In conclusion, diuretics have a relatively weak action and their de nouveau use in pregnancy cannot be recommended. Patients already on diuretic therapy will probably have chronic hypertension mild enough to allow cessation of therapy for the duration of the pregnancy.

What beneficial effect will treatment bring?

Since these drugs have varying modes of action, beneficial results achieved with one preparation may not be seen with another and failure of action of one antihypertensive drug does not mean that all will fail to work. Side effects seen with some medications will not be seen with others. Before giving any patient antihypertensive therapy, the obstetrician must assess whether the patient would benefit from the medication and which drug would be best to use. A diastolic blood pressure of above 110 mmHg appears to increase the risks of morbidity and mortality particularly to the mother and should merit some form of management decision (Turnbull, 1987; Mabie *et al.*, 1987). A diastolic blood pressure above 90 mmHg may constitute a slightly increased risk, especially in the presence of proteinuria (Friedman and Neff, 1975; Butler and Bonham, 1963; Chamberlain *et al.*, 1978b; Naeye and Friedman, 1979; Benedetti, Benedetti and Stenchever, 1982),

but this risk is mostly to the fetus implying the need for increased monitoring. There is not a direct relationship between fetal compromise and blood pressure level.

One therapy, two patients.

In the nonpregnant patient, the potential benefits are balanced against the potential risks of therapy. With the advent of safer drugs with fewer side effects, the use of antihypertensive therapy has greatly increased without any clear evidence of benefit to the patients. In pregnancy, the situation is complicated by the presence of the fetus. Although the benefits of therapy may be directed at the mother, the side effects may be experienced by both the mother and her unborn child. The fear of teratogenicity and other fetal complications has meant that most new drugs are contraindicated for use in pregnancy although there is no evidence of their harm. With the increasing cost of litigation and the relatively low profits from pregnancy use, few companies support or fund antihypertensive studies in pregnancy. This has led to contradictions and other difficulties in this area of research. Labetalol is a drug licensed for use in pregnancy in the United Kingdom but is contraindicated for use in the United States. Both these decisions were based on the same available evidence.

Chronic hypertension

As far as the obstetrician is concerned, chronic hypertension is a non-progressive disease. In the absence of superimposed preeclampsia, there is little increased risk to mother or baby (Redman, 1980; Sibai, Abdella and Anderson, 1983). No study has demonstrated a reduction in the incidence of superimposed preeclampsia by prophylactic antihypertensive therapy. Therefore, the risks of therapy are relatively greater as the benefits are less easily demonstrated. However, the use of antihypertensives in these patients is widely accepted, probably because the patients are often on therapy by the time they are seen by the obstetrician. It is in this situation that the need for treatment should be closely scrutinised. There are some drugs that should be avoided if it is at all possible.

Most of the studies in hypertension in pregnancy have been conducted on chronic hypertensive patients. Methyldopa was assessed in hypertension occurring in pregnancy as long ago as 1968 (Leather *et al.*, 1968). The most comprehensive study of its use in pregnancy was performed by Redman *et al* (1976). They concluded that it was safe and that it appeared to reduce fetal loss from mid-trimester abortions. There was no difference in perinatal mortality rate or the incidence of superimposed preeclampsia. The children of the women who took part in this study were followed up for seven years, and there was no obvious difference between the children from the treatment group, and those from the control group in terms of physical and mental handicaps, behaviour, vision, hearing and intellectual ability, thus emphasising the

drug's safety but also the lack of measurable benefit (Cockburn *et al.*, 1982). These results have led the authors to state that methyl dopa should be the drug of choice in pregnancy as it is proven to be safe. It should be remembered that the other drugs have not been shown to be unsafe. In this study, maternal side effects were troublesome enough to cause 15% of the women to be withdrawn. Another study showed that methyl dopa was associated with reduced neonatal blood pressure (Henderson Smart *et al.*, 1984).

In the 1970's increasing studies have been carried out into the use of β-blockers. Initially, studies with propranolol demonstrated fetal side effects (Lieberman *et al.*, 1978), but more recent work has shown increasing safety (Rubin, 1987; Tcherdakoff and Goupil Colliard, 1983; Tcherdakoff *et al.*, 1978). β-blockers are now well established in the management of chronic hypertension. Metoprolol (Sandstrom *et al.*, 1983), oxprenolol (Gallery *et al.*, 1979; Gallery, Ross and Gyory, 1985; Fidler *et al.*, 1983), labetalol (Lamming and Symonds, 1979; Lardoux *et al.*, 1983b), sotolol (O'Hare *et al.*, 1980), pindolol (Dubois *et al.*, 1982; Lardoux *et al.*, 1983b) and atenolol (Dubois *et al.*, 1982; Lardoux *et al.*, 1983b) have all been used in pregnancy, singly or in combination with vasodilators. Although blood pressure control was achieved with all, few studies showed any measurable benefit to the mother or baby.

Oxprenolol has been compared with methyldopa (Gallery *et al.*, 1979; Gallery, Ross and Gyory, 1985; Fidler *et al.*, 1983). Both drugs had similar effects on blood pressure control, but one study showed that the oxprenolol group had a better outcome in terms of fetal and placental weight (Gallery *et al.*, 1979; Gallery, Ross and Gyory, 1985). These findings were not confirmed by the other study (Fidler *et al.*, 1983). Labetalol was also compared with methyldopa and was found to be as efficient at lowering blood pressure and reducing the progression to proteinuria (Lamming, Broughton Pipkin and Symonds, 1980). There were less side effects found with the β-blockers.

Different β-blockers have been compared. Both pindolol and labetalol have been compared with atenolol in pregnancy (Dubois *et al.*, 1982; Lardoux *et al.*, 1983b). All drugs controlled blood pressure but birth weights were significantly higher in the pindolol and labetalol groups, possibly due to increased uteroplacental blood flow. Atenolol has been associated with intrauterine growth retardation and fetal heart rate abnormalities (Ingemarsson *et al.*, 1984; Dubois *et al.*, 1982; Lardoux *et al.*, 1983b).

Therefore, no great benefit has been shown by the treatment of chronic hypertension in pregnancy. If treatment is desired, no drug appears to be significantly superior, although methyldopa has a high incidence of side effects and the vasodilator β-blockers, oxprenolol, pindolol and labetalol may allow increased fetal growth as

compared to the others.

Preeclampsia (PET)

In preeclampsia, the mother is at risk of vascular, renal, hepatic and neurological damage, all of which are related partly to the hypertension itself (Turnbull, 1987). Therefore, antihypertensive therapy may be of benefit to the mother by reducing these risks. The fetus is at risk from placental damage leading to intrauterine growth retardation and intrauterine death (Chamberlain *et al.*, 1978b). The placental pathology is not directly related to the hypertension as a patient with mild disease may have placental insufficiency and those with severe disease may have a fully functional placenta. Lowering blood pressure is unlikely to improve placental function. However, in these milder forms of hypertension the disease may progress and histological glomerular lesions typical of preeclampsia have been found in pregnant women with only mild hypertension. In pregnancies complicated by hypertension the physiological changes of pregnancy seem to be restricted to the decidual segments of uteroplacental spiral arteries (Robertson, Brosens and Dixon, 1976). These arteries may retain the capacity to respond to vasoconstrictor stimuli. Fibrinoid necrotic lesions are also seen in these arteries after relatively short exposure to high blood pressure (Brosens, Robertson and Dixon, 1970). These lesions are generally worse in women with primary hypertension and superimposed preeclampsia, a situation which carries the highest risk of fetal hypoxia (Robertson, Brosens and Dixon, 1976). All these findings suggest that the rate of progress of the hypertensive disorders in pregnancy may be attenuated by the antihypertensive therapy, allowing prolongation of the pregnancy and greater fetal maturity.

Therefore, the purpose of antihypertensive treatment is; to control the blood pressure, in order to protect the mother from the effects of hypertensive crisis, especially during labour; and to prevent or slow the progression of the disease and prolong the pregnancy sufficiently to avoid the complications of prematurity for the fetus, without increasing the risk to the mother.

Can this be achieved? Are there unacceptable side effects of therapy?

There is controversy about what effect antihypertensive drugs have on uteroplacental blood flow. There is disagreement concerning the ability of the placenta to autoregulate the blood flow (Moawad and Lindheimer, 1982). There is experimental data in rabbits which has shown autoregulation of uteroplacental blood flow throughout a large range of maternal blood pressure (Venuto, Stein and Ferris, 1976). This suggests not only that the placenta can protect itself from the effects of hypertension but also that the blood flow can be maintained after blood pressure reduction.

The effects on the placental flow and the fetus may be dependent on other changes in

the cardiovascular system rather than purely a blood pressure effect. Patients with preeclampsia have alterations in their cardiovascular system. Since vasoconstriction with reduction in the plasma volume is a common finding, it would seem logical to use vasodilator drugs. β-blockers which tend to reduce cardiac output and are beneficial in chronic hypertension may not be as safe in preeclampsia. However, if the plasma volume is low, vasodilators may produce large falls in blood pressure due to the inability of the cardiovascular system to adapt. This would lead to tachycardia and reduction in placental blood flow producing fetal distress. This has been described following the intravenous use of hydrallazine and diazoxide, potent vasodilators (Vink, Moodley and Philpott, 1980; Lipshitz, Ahokas and Reynolds, 1987; Rabau Friedman *et al.*, 1980). Side effects may be reduced by using multiple low doses (MacLean *et al.*, 1981; Nissen, 1982) and concomitant β-blocking agents. Therefore, in patients with preeclampsia, antihypertensive drugs should be used with care and understanding of the underlying problems. Lowering the blood pressure does not cure the disease and continuing vigilance of the mother and fetus is required, usually as an inpatient. Preeclampsia is a progressive disease and antihypertensive drugs will only slow the progress at best. Although there is now a wide experience of drug therapy in preeclampsia there are still conflicting views on their benefits.

Severe hypertension.

There has been no randomised study that has evaluated treatment in severe hypertension although there is general consensus about starting hypotensive treatment when diastolic blood pressure is above 110 mmHg. This is to protect the mother from cerebral vascular accident, the largest cause of maternal death in hypertensive disease of pregnancy. Many centres manage severe hypertension with prophylactic anticonvulsant therapy, particularly magnesium sulphate. As many as 18% of all patients may be given this therapy although magnesium sulphate also has not been evaluated by controlled trial (Pritchard and Pritchard, 1975). Its role in established convulsions would appear to be beneficial. However, outside the United States, magnesium sulphate is not so widely used, with less than 20% of obstetricians in the United Kingdom having any experience with it (Chamberlain *et al.*, 1978a). Sedation with valium and chlormethiazole is often used in the UK.

If antihypertensive drugs are to be used, hydrallazine is still the most commonly used in acute hypertension, given intravenously by injection or infusion (Garden, Davey and Dommisse, 1982). Diazoxide has largely been superseded by more recent antihypertensives because of its recognised side effects. Satisfactory control of the blood pressure was easily achieved with intravenous infusion of labetalol in severe hypertension in pregnancy (Michael, 1979; Michael, 1986). There were no maternal

hypotensive episodes or side effects. A slow intravenous injection of 50 mg of labetalol is an effective treatment of severe hypertension. It has been shown to minimise the normal hypertensive effect of intubation at caesarean section (Ramanathan *et al.*, 1988).

Nifedipine has also been proven effective in pregnancy and the puerperium (Walters and Redman, 1984; Barton, Hiett and Conover, 1990). On comparison with hydrallazine, nifedipine has been found to be as effective in lowering blood pressure and has the advantage of being an oral therapy (Seabe, Moodley and Becker, 1989). One possible serious problem is the possible interaction between calcium channel blockers and magnesium sulphate leading to sudden excessive fall in blood pressure (Waisman *et al.*, 1988).

Mild to Moderate hypertension

It is less well accepted that treatment should be started with diastolic blood pressure between 90 and 100 mmHg. There is no universal agreement as to whether drug treatment is preferable to; doing nothing,; bed rest; or delivery, in women with mild to moderate preeclampsia. However, the use of drugs to control blood pressure in pregnancy is gradually increasing, due to the greater knowledge about the drugs and their safety in pregnancy.

Despite the initial reservations, adrenoceptor antagonists have now been studied fairly extensively in preeclampsia, and they have been shown to be both safe and effective in controlling blood pressure. They are also relatively free of side effects, making them acceptable to patients.

The first randomised controlled study of an adrenoceptor antagonist in preeclampsia was performed with atenolol, a selective β-receptor antagonist (Rubin *et al.*, 1983). This was a study of 120 women. Atenolol effectively controlled blood pressure and reduced the subsequent development of proteinuria, suggesting a possible beneficial effect on the disease process. It is not a surprise, however, if antihypertensive therapy reduces the incidence of proteinuria (Rubin *et al.*, 1983; Lamming, Broughton Pipkin and Symonds, 1980), as this is probably a result of the reduction in the perfusion pressure to the kidney.

There was no difference in fetal and neonatal complications such as intrauterine growth retardation, neonatal hypoglycaemia or hyperbilirubinaemia between the two groups. Respiratory distress was seen only in the control group. However, neonatal bradycardia was more common in the atenolol group, although there was no effect on neonatal blood pressure. The children from this study have all been followed up for one year and atenolol has not been shown to have any adverse effects on their development. Other studies have confirmed these findings. Some workers recommend the use of a vasodilator like nifedipine as concomitant therapy to

overcome the vasoconstriction of preeclampsia (Constantine *et al.*, 1987). Labetalol, which has built in vasodilator ability, has also been shown to be effective.

It would seem from these studies that adrenoceptor antagonists are both safe and effective in the treatment of preeclampsia, and may have some beneficial effects on the disease process. Whether any particular adrenoceptor antagonist is more effective than the others is not certain. Labetalol has been shown to be as good as or superior to methyl dopa (Lamming, Broughton Pipkin and Symonds, 1980), while both labetalol (Lardoux *et al.*, 1983a) and pindolol (Dubois *et al.*, 1983) appear to have advantages over atenolol.

Hydrallazine is frequently used as a "second line" drug to augment the effects of adrenoceptor antagonists and methyldopa when satisfactory control is not achieved with a single agent. Erratic metabolism yields unpredictable responses by the oral route and nifedipine has largely superseded hydrallazine.

Metabolism of drugs in pregnancy

Pregnancy is associated with major changes in the maternal metabolism. Various studies have shown that there is an alteration in the way a pregnant woman handles antihypertensive drugs. The plasma half life appears to be altered and the length of time the drug is effective is shortened (Rubin *et al.*, 1983; Rubin *et al.*, 1987; Rogers, Sibai and Whybrew, 1990). This may lead to the need for different dosage regimes for the pregnant compared with the non-pregnant.

Other effects antihypertensive drugs may have.

Very few drugs are used for the reason for which they were first produced. The antihypertensive action is often stumbled upon during evaluation studies. Therefore, it is not surprising when other effects are discovered. The most consistent is an antiplatelet action shown by propranolol, pindolol and labetalol (Greer *et al.*, 1985b). Labetalol has also been shown to reduce thromboxane production (Greer *et al.*, 1985a). This result is probably not a beta-blocker effect as the nonhypotensive isomer of propranolol is associated with the anti-platelet effect.

Discussion

There is no doubt that hypertension in pregnancy is associated with an increased risk to the mother and fetus. However, there appears to be no consensus concerning the best treatment regimes. It appears clear that many of the patients do not require special care but vigilance is probably required to distinguish those that do from those that do not. Hospitalisation is not necessary for all. Lowering blood pressure appears to be possible and easy to achieve. But does it bring benefit?

As therapy during pregnancy is directed at the mother, there is concern that the fetus might be subjected to adverse effects without benefit to itself. If antihypertensive therapy prolongs pregnancy, the fetus will indirectly benefit from this and this may

counter balance any harmful effects. Not all therapies would appear to be beneficial and some drugs have greater side effects than others. Close monitoring is required for any fetus of a hypertensive mother and this need is heightened if she is given antihypertensive therapy. It is difficult to distinguish between side effects produced by therapy and the problems of the disease itself. All drugs will cross the placenta to a greater or lesser degree. It has been reported that some babies have a prolonged clearance of labetalol after delivery (Haraldsson and Geven, 1989). Atenolol has a prolonged neonatal clearance. It would be surprising if these drugs produced no side effects in the neonate.

The ACE inhibitors appear to produce direct complications that are harmful to the fetus and neonate. There would have to be strong reasons for their use in pregnancy. Diuretics have only a weak effect and the potentially harmful changes to placental blood flow would count against their use.

Atenolol is a very effective drug in pregnancy, especially in those with an increased cardiac output, but there are reports of fetal heart rate abnormalities, high levels of cord blood drug concentration and a slow neonatal clearance. One of the main fears concerning antihypertensive drugs is the effect they might have on the placental blood flow. Labetalol has been shown in both animal and human studies to lower blood pressure and maintain placental blood flow. Hydrallazine and nicardipine have been shown to reduce placental blood flow but nifedipine does not. It is difficult to know whether these findings are clinically relevant but it would appear advisable to use drugs that have not been shown to have adverse effects.

All the β-blockers are known to be associated with hypoglycaemia, bradycardia, and hypotension in some infants. This does not appear to be clinically significant. These problems are also common in babies born of hypertensive mothers not on therapy. It is difficult, therefore, to distinguish the side effects of drugs from manifestations of the disease process. If widespread use of medication is to be carried out, close monitoring is required.

3.5 Conclusions

1) The majority of hypertensive patients are at relatively **low risk** and do not require therapy.
2) Antihypertensive drugs are mostly **safe** in pregnancy but their role is **unproven.**
3) Drug treatment may be beneficial to **lower blood pressure** and minimise the risks for the mother.
4) The combined alpha/beta blocker **labetalol** appears to be well tolerated and may have some benefits over the others.

5) Lowering the blood pressure may **moderate** the progression of the disease but it **does not stop it.**
6) Care should be taken to **monitor** closely the mother and the fetus.
7) **Delivery** remains the only cure for established preeclampsia.
8) **Side effects of beta-blockers** for the neonate include hypoglycaemia and occasionally bradycardia.
9) Once delivery has been carried out the **therapy** may need to be **continued** in some patients for a number of weeks.
10) If blood pressure does not settle following delivery the **diagnosis may need to be altered** and the patient referred for further assessment.

CHAPTER 4

The Changing Face of Eclampsia in The Glasgow Royal Maternity Hospital 1933-1983

4.1 Introduction

In eclampsia, mortality and morbidity for both mother and infant have been reported as being high (Wightman, Hibbard and Rosen, 1978; Pritchard and Pritchard, 1975; Lopez Llera, Linares and Horta, 1976; Zuspan and Ward, 1965). The cause of maternal death was usually cerebral vascular accident (Lopez Llera, Linares and Horta, 1976). Abruptio placentae and prematurity were the main causes of perinatal death (Wightman, Hibbard and Rosen, 1978; Pritchard and Pritchard, 1975). Much of the work that has been published is from parts of the world where eclampsia is still commonplace. It would appear that, in the UK, the number of cases seen each year has been falling and the prognosis for both mother and infant has improved. It would appear logical to assess the risk in our own population, and design management protocols accordingly.

The Glasgow Royal Maternity Hospital (GRMH) is a large maternity hospital which has served Glasgow for over 150 years. It serves a large catchment area consisting mainly of social class IV and V patients. Any obstetric problems such as eclampsia have always been referred to the hospital. Detailed hospital records for the last 50 years are available, giving the number of deliveries and outcome of the pregnancies, including all those patients delivered within the surrounding district and not within the hospital. It provides an ideal centre to investigate the changing incidence of eclampsia and its concomitant maternal and fetal morbidity and mortality. To study the effect of eclampsia on maternal and fetal morbidity in GRMH, it was decided to review all the cases of eclampsia presenting to the hospital over the 50 year period 1933-1982.

4.2 Methods

The case records of all the patients presenting with eclampsia over the fifty year period of 1933-82 were studied if they were available. If no case records were available, information was taken from the yearly hospital reports. These reports contained all the relevant information about the patients presenting with eclampsia during the year. The statistics concerning number of deliveries, the maternal death rate and perinatal mortality for the hospital and district were noted. The total numbers of eclamptics, maternal deaths and deliveries for the whole district were available throughout the time period. Although the catchment area has changed with the opening of other maternity hospitals, there is no reason to believe that those patients lost to the catchment area would be any different than those remaining. Therefore, although the actual number of patients delivered under direct supervision of the hospital has decreased over the study period, this should have little effect on the incidence of eclampsia in the patient group within the area of Glasgow served by the hospital.

4.3 Results

Over the study period 271,752 infants were delivered within the hospital or surrounding district. The number of deliveries occurring in the hospital remained almost constant for each decade, whereas deliveries in the district decreased since 1943 (Table 4.1).

1,118 cases of eclampsia were managed by the hospital staff over this time. The number of cases and the incidence of eclampsia has significantly fallen over the period of the study (Table 4.1). The ratio of primigravidae to multiparous patients with eclampsia remained similar throughout each decade studied (Table 4.2). Overall, antepartum eclampsia was the most common type of presentation seen. This was followed by intrapartum and post partum cases (Table 4.3). There has been a change in the proportion of these presentations between the first two decades and the last three. (Fig.4.4) The relative proportion of postpartum cases has significantly increased ($p<0.001$) and the proportion of both antenatal ($p<0.05$) and intrapartum cases reduced ($p<0.05$). This implies that there has been a smaller reduction in the postpartum cases than in the others.

If the overall incidence of preeclampsia is assumed to be 15%, there would have been around 11036 preeclamptics in the first decade, giving an incidence of one eclamptic patient per 20 cases of eclampsia. In the last two decades, there will have been around 14120 preeclamptics, giving an incidence of one eclamptic patient per 152 preeclamptics. In the last decade, the figure is 1 per 292 preeclamptics. Although this is only an estimate of the incidence, it does suggest that the risk of eclampsia is now much reduced from the levels seen previously.

Management

From Table 4.5, it can be seen that treatment of eclampsia altered considerably over the fifty year study period. In the first decade studied, the mainstay of treatment was delivery of the patient, and this often included induction of labour using cervical bougies under full anaesthesia. Sedation was achieved by chloroform, morphine and phenobarbitone. Stomach and colonic lavage with magnesium sulphate was used to clear the patient of 'toxins'. Various medical therapies were instituted in the ensuing years, including Stroganoff therapy and bromethol. It is only in the most recent years that true anticonvulsants and antihypertensives have been employed in the management of eclampsia.

In the last decade studied 78% of patients received diazepam, 94% chlormethiazole and 78% received a hypotensive agent, usually hydrallazine. Only six patients received treatment prior to the onset of seizures and in only one of these cases did the patient receive an antihypertensive drug.

Maternal Mortality and Morbidity

The maternal mortality rate associated with eclampsia has reduced dramatically from the first to the last decade (Table 4.6). Since 1952, there has been significant reduction in the maternal mortality rate (Table 4.7) This is true not only for the absolute numbers but also for the incidence of death in eclamptic patients. There has been no maternal death from eclampsia since 1964.

The causes of death in 116 of the women who died from eclampsia during the period studied was previously reported (Govan, 1961). There were 68 primigravidae and 48 multiparous patients. 69 patients were less than 30 years of age and 47 were over 30 years of age. The actual cause of death was established in 110 of the 116 cases. Cerebral lesions accounted for 39 cases, 32 of which showed a large haemorrhage in the pons and basal nuclei. In 47 cases the cause of death was due to cardiorespiratory failure. Sometimes the cardiac failure occurred during or immediately after the eclamptic phase but frequently death was due to subsequent pneumonia. Massive adrenal haemorrhage was found in 3 cases , sepsis caused death in 4 cases, delayed chloroform poisoning following Stroganoff treatment accounted for four and signs of shock a further eight. Renal impairment was a relatively rare case with uraemia occurring in only 5 cases. Analysis of the cardiorespiratory group and comparison with those dying of cerebral haemorrhage revealed a difference between the onset of convulsions and death. In the cerebral group the average time lapse was 23 hours compared with 43 hours in the cardiorespiratory group. It was also found that the incidence of prodromal symptoms did not differ and both groups had an average of 7 seizures. Another interesting finding was that chronic pyelonephritis was a frequent complication in these patients.

Clinical Findings 1973-82

The 19 cases of eclampsia in the last decade were studied more closely. The most common premonitory symptoms were those of headache, visual disturbance and abdominal pain. However, only nine patients demonstrated these prodromal symptoms. Five patients arrived at the hospital in a semiconscious or unconscious state and nine patients had their seizures outside the hospital. These included fits in other Casualty Departments, at home or in the general practitioners surgery. The other ten patients seized for the first time in the hospital but only one of these occurred prior to delivery.

Only eight of the nineteen patients had documented evidence of hypertension prior to convulsing. Four of the 10 antepartum cases had a documented rise in blood pressure prior to the seizure. Two of these patients were noted to be hypertensive at the antenatal clinic but refused admission and were later admitted unconscious from home. One patient had essential hypertension and was on treatment with

methyldopa but had seizures at home. The other patient was in hospital with severe pregnancy induced hypertension. She was not treated with antihypertensive therapy and convulsed while in the hospital. Three of the intra and post partum eclamptics had documented rises of blood pressure prior to the seizure and none were treated with antihypertensives although two were given sedative agents.

Of the 19, only 2 had significant morbidity. One patient who had been known to have essential hypertension was later diagnosed as having Conn's syndrome. Another patient who delivered a fresh stillbirth after intrapartum eclampsia subsequently developed low grade disseminated intravascular coagulation and acute renal failure which resolved after treatment. This was the only patient in the last decade of the study who had evidence of abruptio placentae.

Fetal Outcome

There has been a steady decrease in perinatal mortality due to eclampsia (Table 4.8). This reaches statistical significance after 1963 (table 4.9). The perinatal mortality rate of eclamptics per 1000 hospital births has also reduced. The proportion of stillbirths to the eclamptic perinatal mortality rate fell during the fifty year period and neonatal deaths now form a larger percentage of perinatal mortality rate (Table 4.9).

Fetal Outcome 1973-1982

There were 21 infants, including two sets of twins, born to the 19 eclamptic patients. Three infants were stillborn and there were four neonatal deaths. 14 infants including both sets of twins survived. Six of the seven fetal losses occurred in patients with antepartum eclampsia. The mean gestation of the two stillbirths which occurred in the antepartum group was 28 weeks and the mean birth weight was 1.5 kg. The mean gestation of the four neonatal deaths in the antepartum group was 29 weeks and the mean birth weight was 1.33 kg. The one other fetal death was a stillbirth in a patient at term with intrapartum eclampsia. This patient had a seizure while a fetal blood sample was being performed for fetal distress. There was delay in performing a caesarean section and a fresh stillbirth weighing 3.18 kg was delivered. There were no losses in patients with postpartum eclampsia.

The mean gestation of the 14 surviving infants was 39 weeks and the mean birth weight was 2.8 kg. None of the 21 babies were below the 10 th centile for birth weight for their gestational age.

4.4 Discussion

In any retrospective case record study, there is a risk that changes seen can be due to factors other than disease changes. Great care was taken to include all the sources of information available on the deliveries in the hospital and the district. Therefore, the author is sure that the denominator of total deliveries is accurate. Although, the

exact area of referral has altered of the last fifty years, this is inevitable in a shifting population and developing health care system. It is only in the last decade that particular referrals to the Glasgow Royal Maternity Hospital have been made from other hospital areas because of particular facilities available. Therefore, there is no reason to believe that the population cared for has significantly changed in type over the fifty years. It is difficult to know whether the referral of eclamptics into GRMH was always 100% in the early years. Some may not have been counted. This would tend to underestimate the rate in the earlier decades making the changes seen even more significant. Therefore, it is felt that both the value of the denominator and the total number of eclamptics are reasonably certain. It is therefore possible to calculate the changing rates of eclampsia over the last fifty years.

Cruickshank (1923) reported the high incidence of the toxaemias of pregnancy in Glasgow. At that time, no other centre in the United Kingdom, Europe or the United States of America reported such a high incidence of those conditions. Over the study period, the incidence of eclampsia fell from 729/100,000 to 51/100,000 deliveries from the first to last decade studied. This later figure is compatible with other publications (Campbell and Templeton, 1980).

The ratio of primigravidae to multipara was similar throughout the decades of between 2 and 3 to 1. This has been reported by other authors (Wightman, Hibbard and Rosen, 1978; Campbell and Templeton, 1980; Cruickshank, 1923). This suggests that multigravid women are also at risk, albeit lower. Since this constant ratio is seen against a background of reducing proportion of multigravid deliveries, it would imply that the relative risk to the parous woman may be increasing. Accurate figures for primigravid and multigravid delivery numbers were not available, and this change in incidence could not be studied. The long term prognosis for multigravidae who develop eclampsia, has been shown to be worse than in those women developing eclampsia in their first pregnancies. In a study of longterm follow up, a much higher proportion of those who had eclampsia as a multigravida were found to have died from cardiovascular disease than did those women who had eclampsia as primigravida. Cardiovascular causes accounted for only 29% of the remote deaths of the primigravid eclamptic women, as compared with 82% of those who were multigravid (Chesley, Annitto and Cosgrove, 1976).

The highest maternal mortality occurred in patients with antepartum eclampsia and this has been reported by other workers (Lopez Llera, Linares and Horta, 1976).

Chronic renal disease, particularly pyelonephritis was a common finding in fatal eclampsia. In patients over the age of 30, chronic vascular disease was a frequent occurrence and massive cerebral haemorrhage was more common in this age group. (Govan, 1961). The prognostic importance of age has previously been noted (Davies,

1971; Hibbard, 1973; Lopez Llera, 1967; Lopez Llera, Linares and Horta, 1976). It is suggested that either age reduces the adaptability of vital systems to various types of pathogenic influences and stress or that older women are more likely to have preexisting disease that predisposes to eclampsia.

The falling maternal death rate was one of the striking features in this study. The reduction in the incidence of the condition has resulted for several reasons. The most dramatic changes in incidence and mortality from eclampsia occurred in the 1950's. Around this time there was a gradual move towards hospital based obstetric care. There were major improvements in social circumstances and the National Health Service was developed leading to improved antenatal care and hospital facilities. The introduction of bromethol as a eclamptic therapy, also occurred in the mid/late forties. Therefore, the falling incidence is likely to be related to a combination of improved social conditions, better antenatal care, increased intervention therapy and earlier delivery leading to less progression to eclampsia.

Treatment of eclampsia has altered considerably over the 50 year study period. The most common drugs used in recent years were diazepam and chlormethiazole. Antihypertensive agents were not frequently used. Only one of the 19 eclamptic patients in the final decade received an antihypertensive drug prior to seizing. In two cases, if hypotensive therapy had been commenced then seizures may have been prevented. The lack of use of hypotensive agents has been reported by others (Wightman, Hibbard and Rosen, 1978) when only 12% of eclamptic patients received a hypotensive drug and 25 permutations of drugs were used to treat 43 patients. The recent reports on maternal death in England and Wales also noted the lack of antihypertensive therapy (Turnbull *et al.*, 1989). Although, in in this triennium, cerebral vascular accident (CVA) was still a major cause of maternal death, cardiopulmonary problems were now the biggest cause. If CVA was to blame, this tended to happen early following the convulsion. Cardiopulmonary problems occurred later. This would suggest that antihypertensive drugs may be an important first line therapy but problems of fluid balance follow this. Renal failure occurred in less than 5% of cases.

Eclampsia continues to be a major cause of perinatal death worldwide (Wightman, Hibbard and Rosen, 1978; Turnbull *et al.*, 1989; Sibai, 1990). Despite an overall fall in perinatal mortality due to eclampsia, the disease is still associated with a fetal loss of 182/1000 in the relatively few cases seen in the last twenty years. Over the 50 year study period, the ratio of stillbirths to neonatal deaths has been reversed, with the latter now representing a larger percentage of the perinatal mortality. In the last decade, of the seven infants who died, four were neonatal deaths all occurring in patients with antepartum eclampsia. The mean gestation at time of delivery was 29

weeks, reflecting that prematurity was a significant contributor to fetal loss. With the improvement in neonatal care over recent years, many of these infants would now be expected to survive in a tertiary care neonatal unit. Of the three stillbirths, two would now be potentially preventable. One was a termination of pregnancy because of severe hypertension and the stillborn infant weighed 1.1 kg. Such a case would be managed differently now with antihypertensive therapy and delivery by caesarean section if further deterioration occurred. A favourable outcome could be anticipated in an infant of this birth weight. The other stillbirth could have been avoided, had a caesarean section been performed earlier. One case resulting in a stillbirth was probably unavoidable. The patient presented at another hospital in an unconscious state. By the time of transfer to the maternity hospital no fetal heart was detected. It was interesting to note that this patient's mother had a history of having a cerebrovascular accident during pregnancy, attributable to eclampsia. Overall, the perinatal loss in the last decade of the study is disturbing. However, the majority of the fetal loss was related to prematurity and in current day practice, many of these infants would probably have survived.

None of the surviving nor the fetal loss cases showed evidence of growth retardation as measured by birth centile. This perhaps reflects the acute presentation of the majority of the patients and the fact that a preceding preeclamptic process with resultant placental insufficiency was not seen in any of the patients during the last 10 years of the study. The lack of evidence of growth retardation is contrary to the experience of other authors (Sibai, 1990; Wightman, Hibbard and Rosen, 1978). and may reflect the inaccuracy of the methods of diagnosis rather than lack of growth retardation. A properly designed case control study might help to answer this question.

Evidence of abruptio placentae was rare in the eclamptic patients during the last decade of the study. The incidence was similar to that reported by Sibai when 9 of 67 patients had evidence of abruption (Sibai, 1990).

The falling incidence of eclampsia is probably due to multiple causes, including improvement of general health, antenatal care, reduction in parity and improvement in the treatment of hypertension. However, despite a low maternal mortality and morbidity, fetal loss from eclampsia is still relatively high, due mainly to prematurity. The general trend in improved neonatal survival for the premature infant should lead to better prognosis for infants born to eclamptic mothers.

4.5 Conclusions

The main conclusions are:

1) The incidence and therefore the **risk** of eclampsia has dramatically fallen.
2) **Multigravid** patients are also at risk of developing eclampsia.
3) There has been a **relative increase in the rate of postpartum eclampsia** compared with ante and intrapartum eclampsia.
4) The risk related to postpartum eclampsia is less than that related to antenatal eclampsia.
5) **Renal failure is a rare** cause of maternal death.
6) Cardiopulmonary problems occur between 40-48 hours after convulsions
7) Despite the steady reduction, there is still a **high rate of fetal loss** that may be preventable.
8) There was sometimes a failure to deliver the baby in the **best possible condition** and the **best possible way.**
9) The risk of abruptio placenta and coagulation defects would appear to be low.

CHAPTER 5

STUDIES INTO THE CHANGES OF BLOOD PRESSURE AND BLOOD PRESSURE VARIATION DURING PREGNANCY

5.1 Introduction

Hypertension in pregnancy has well recognised complications of morbidity and mortality for both mother and baby. It also constitutes a high percentage of antenatal admissions. However, there is a gross overdiagnosis of the condition with almost 60% of patients being found not to be hypertensive when admitted to hospital even though the blood pressure was elevated at the outpatient clinic (Hall, Chang and MacGillivray, 1980).

Blood pressure is not a precise physiological measurement but a continuum (Pickering, 1968). In any given individual, it varies on a minute to minute and hour to hour basis. It is also known to vary throughout pregnancy (MacGillivray, Rose and Rowe, 1969). Despite these recognised changes, arbitrary values are used as markers of abnormality and hence for management decisions. These levels have been decided partly following statistical analysis of normality and partly related to the adverse outcome associated to the elevation of blood pressure (Friedman and Neff, 1975; Friedman and Neff, 1977; Friedman and Neff, 1978).

These arbitrary values are widely accepted. Many obstetricians would wish to admit to hospital, patients whose diastolic blood pressure has reached 90 mmHg. Others would intervene with either antihypertensive drugs and/or delivery if the diastolic blood pressure reached 110 mmHg (Chamberlain *et al.*, 1978a; Trudinger and Parik, 1982; Turner, 1981; Redman, 1987).

Many of the patients with blood pressures above 90 mmHg do not have any problem. Therefore, using a diastolic of 90 mmHg as the cutoff point for the diagnosis of hypertension in pregnancy would appear to be an overdiagnosis (Hall, Chang and MacGillivray, 1980). There could be several reasons for this. Despite the known blood pressure variation (Murnaghan, 1987; MacGillivray, Rose and Rowe, 1969), single blood pressure readings are often used to make the diagnosis. Alternatively, the measurement is repeated until a value is obtained which is below the arbitrary action level. This is then taken as the "true" level. There are no guidelines available that would let clinicians know the accuracy of a single blood pressure, the value of repeated readings or whether an average of these readings would be more useful.

There are changes in the blood pressure levels throughout pregnancy. It would appear to be illogical to use the same blood pressure level as abnormal at all times during pregnancy.

These doubts concerning the accuracy of the diagnosis of hypertension in pregnancy has led to the development of outpatient Day Care Assessment units (Walker, 1987; Rosenberg and Twaddle, 1990), various outpatient tests using automated blood pressure monitoring (Mooney and Dalton, 1990) or home visiting of community midwives (Matthews, Patel and Sengupta, 1971; Rosenberg and Twaddle, 1990) as a

method of assessing the risk to the individual patient. The purpose of these regimes is to try and differentiate between those who require hospital admission and those who do not. Clear guidelines at the initial point of diagnosis might reduce the overall workload.

5.2 Aims

The aims of the studies described in this chapter were to investigate the variation of blood pressure during pregnancy, the accuracy of a single blood pressure reading, how many times this reading would have to be repeated to get a reproducible average, and whether automatic blood pressure equipment gave a more accurate result.

5.3 Blood pressure changes throughout pregnancy.

MacGillivray (1969) showed that blood pressure fell in the first and second trimester and rose again towards term (Fig.3.1). This study was done on primigravida only. In order to confirm these changes and compare them with the changes found in multipara, the blood pressures in 186 primigravida and 115 multiparous randomly selected patients attending the antenatal clinic at the Glasgow Royal Maternity Hospital were measure serially throughout pregnancy.

Methods

All patients were resting for 10 minutes prior to the measurement and sitting at 45 degrees. The blood pressure was taken in the right arm using a London School of Hygiene random zero sphygmomanometer at the level of the heart. Phase four diastolic was used throughout. All the readings were carried out by one of two investigators. All patients were included in the results and were not excluded if their diastolic blood pressures rose above 90 mmHg.

All measurements were carried out between the hours of 9 a.m. and 12 noon to try and standardise the patient groups and to make sure the variations were not related to the diurnal rhythm (Murnaghan, 1987).

Results

The demographic data of the two groups are shown in Table 5.1. As would be expected the multiparous group were older than the primigravida. The results are shown in Figure 5.1. The graph confirms the fall in blood pressure in the second trimester with a rise towards term as previously described (MacGillivray, Rose and Rowe, 1969). However, it was found that the parous women had a significantly lower systolic and diastolic blood pressure in mid-pregnancy as compared to the primigravida (Significance shown in Table 5.2). This difference persisted until the last weeks of pregnancy.

Discussion

These findings were not expected. There was no difference between the groups at the beginning or the end of pregnancy, but there was a significant difference from 24 weeks onwards. It is surprising that the multiparous patient had lower blood pressures than the primigravida as blood pressure normally rises with age. Since the fall in blood pressure is associated with vasodilation (Easterling *et al.*, 1990), these findings suggest that the multiparous patient has greater vasodilation and for longer than the primigravida. This would imply a greater adaption to pregnancy in the multiparous patient which may help to partly explain the reduced incidence of preeclampsia.

Since the blood pressure alters throughout pregnancy and between primigravida and multipara, it is difficult to decide on any particular blood pressure level that may offer a simple cut-off point between normal and abnormal. The level must have a different significance in different parities and at different gestations.

5.4 Blood pressure variation at the outpatient clinic.

Management decisions are often based on a single blood pressure reading. Alternatively, the measurement is repeated to assess the "true" value after rest. There is little information on the repeatability of blood pressure readings and whether this second reading is any more accurate than the first. The purpose of this study was to study the reproducibility of an outpatient blood pressure reading.

Methods

Three hundred and sixty five randomly selected primigravidae in the third trimester attending the routine antenatal clinic were asked to volunteer for the study. All patients were lying semi-recumbent on the examination couch and the blood pressure was taken in the right arm using a London School of Hygiene random zero sphygmomanometer at the level of the heart. Initial blood pressure was taken and this was repeated within 10 minutes. All estimations were carried out by the same observer. Both values were noted and used for analysis of variation. Primigravidae in the third trimester were used as this is the patient group where the diagnosis of blood pressure is seen as the most relevant.

The difference between the two readings was noted and whether it was higher or lower than the first reading.

Results

The range of systolic blood pressures is shown in Figure 5.2. and the range of diastolic blood pressures in Figure 5.3. There is a normal distribution in both systolic blood pressures and no difference between the means or ranges of the two readings. Therefore there was no difference between the readings when the group was looked at as a whole.

If the individuals were studied, there was marked differences found. Less than 40% of the patients had a repeated systolic or diastolic measurements within 5 mmHg of the original blood pressure reading (Figure 5.4). In some, the difference was considerable. This measurement could be either higher or lower than the original measurement.

Discussion

These findings have considerable significance. If the blood pressure of different groups are being studied, a single blood pressure from each individual is adequate to calculate the blood pressure mean. However, if an individual is being studied, a single blood pressure only gives an approximation of the patient's blood pressure. If the first is found to be elevated, a repeat sample may be lower. This appears to be signs of the normal fluctuation and not an effect of rest. There is no evidence to suggest that the second reading is any more 'correct' than the first. Similarly, if a patient with a 'normal' blood pressure is checked again, the level may be higher. It would appear that repeated measurements may give a better idea of the patient's blood pressure range. From this an average could be calculated and used as the 'true' blood pressure.

5.5 Blood pressure variation in the patients attending Daycare.

What is not known from the above study is the effect of the level of the initial blood pressure on the variation seen. Also, if an average of several blood pressures are to used, what is the number of blood pressure readings required to give a mean which would be a reasonable estimation of the patient's 'true' blood pressure. In order to try and answer these questions one thousand primigravidae attending the Daycare Assessment Unit (see Chapter 7) for the first time in the third trimester were studied.

Methods

Five separate blood pressure readings were taken between 9 and 12 noon on the morning of attendance by the attendant nursing staff. All patients were resting for 10 minutes prior to the measurement and sitting at 45 degrees. The blood pressure was taken in the right arm using a mercury sphygmomanometer at the level of the heart. These were part of the routine monitoring of the Daycare patients by the attendant nurses who were not aware that a study of the variation was to be carried out. Therefore, there was no bias due to the nurses trying to achieve equality of readings. The diastolic blood pressure was assessed using the phase four Korotkoff sound. The 5 blood pressure readings were compared for degree of variation, the effect of the starting blood pressure on this variation, whether there was a trend from the first to last blood pressure and for the number of blood pressure readings required to give a mean which would be a reasonable estimation of the patient's 'true' blood pressure.

Results

The blood pressures in this study were higher than in the normal study. This is not surprising as the patients were originally referred because of hypertension. The

ranges found with the first and second readings of both systolic and diastolic blood pressure were similar (Figures 5.5 and 5.6). There was a small but significant difference in the means of the readings suggesting a small reduction between the first and second readings. These differences were only 2.5 mmHg for the systolic blood pressure and 1.3 mmHg for the diastolic blood pressure. This does not appear to be clinically significant. Similarly to the previous study, the blood pressure readings showed a very wide variation (Fig 5.6). In less than 50% of the patients was the second blood pressure within 5 mmHg of the first. The differences could be either up or down. There is always a risk that there is a bias towards readings ending in 5 or 0 when the blood pressures are carried out using an open method. In this study there was an predominance to readings ending in 0 and 5 (Figure 5.8) but there was a reasonable scatter of results. It would appear that generally the midwifery staff took care to take an accurate reading.

The degree of variation was compared with the level of the first measurement (Figure 5.9 and 5.10). The results demonstrate that for the higher initial blood pressures there is a tendency for the blood pressure to fall (a positive difference) and the lower blood pressure to rise (a negative difference). These are highly significant differences ($p<0.001$). This would appear to demonstrate "a tendency towards the mean" where repeated values would tend towards the mean of the group as a whole. If the second and third, third and fourth or fourth and fifth readings are studied, the results are fundamentally the same with similar variations found. There is no evidence of "stabilisation" over these five readings.

If the complete group was studied, there was no trend from the first reading to the fifth reading apart from the small but significant difference between the first and second readings previously mentioned. (Fig. 5.11). This does not support the argument that patients' blood pressure will fall as they get used to the person taking it. This confirms the findings of the previous study where the results of the group as a whole showed no change despite the variations seen in the individual.

If the single reading does not give an accurate assessment of the patient's blood pressure, is an average of several readings any better.

In order to try and answer this question, the first two and subsequent blood pressure readings were averaged and compared (Fig. 5.12). The average difference between the first two readings was 7.4±8.3 mmHg. If a third reading was added to the first two and averaged, the difference between this result and the average of two readings was 2.9± 4.8 mmHg. The addition of a fourth and fifth reading further reduced difference although these changes did not reach statistical significance.

Although the average difference may not be great, what is more important is the number of patients where the difference is still significant. Figure 5.12 shows that

with the increasing number of blood pressures used to calculate the means, the standard deviations got smaller implying a reduced number of patients with persistent larger differences. If an arbitrary difference of less than 5 mmHg is taken as acceptable, The percentage of those with a persistently higher difference was noted. The results are shown in figure 5.13. If the first two readings are compared, over 40% of the patients had a difference of 5 mmHg. If the average of the first two readings is compared with the average of the first three, there are still 10% of the patients with a difference of more than 5 mmHg. This means that an average of two readings is only accurate in 90% of the patients. If the difference between three and four readings are compared, 98% of the patients had a difference of less than 5 mmHg. An addition of five readings appeared to give little benefit. Therefore, an average of three readings appears to give reasonable accuracy in most patients and four readings in almost all.

Discussion

This study confirms the findings of the outpatient study. There is no difference in the means of the repeated blood pressure readings in the given group of patients although the blood pressure in any individual patient can vary considerably. The direction of the variation is related to the starting blood pressure. Therefore, it would not be surprising if a patient who is found to have a high blood pressure reading is found to have a lower blood pressure reading on repeating the measurement. Similarly a patient with known elevation may be found to have a lower reading but the next reading will probably be elevated again. The blood pressure fluctuates around a given mean. However, this might not always be true as some patients will get worse and others get better. A series of three or four measurements should give that information and the mean of the readings will be a reasonable estimate of the "true" blood pressure. Future readings will vary round this mean. This study suggests that the mean of three readings is the minimum that should be used and four readings is preferable. Management decisions should not be taken on single high or low levels. The more often a blood pressure is taken, the more likely the extremes of the range will be found. Therefore, in a patient with moderately high blood pressure, if the readings are repeated often enough, a 'normal' reading of less than 140/90 mmHg will be achieved. This is not the true, rested blood pressure but the lower extreme of the range. Similarly, a single reading of 160/110 mmHg will probably be the upper extreme of the range. Only persistent elevation or an elevated average blood pressure should be taken as significant. Nelson stated that two readings of the diastolic blood pressure above 110 mmHg are required before a diagnosis of severe preeclampsia can be made (Nelson, 1955b).

If an average blood pressure is clinically useful, can an automated blood pressure

recorder be used to calculate it?

5.6 Blood pressure variation using the Dinamap automatic blood pressure recorder.

The same 300 patients attending Day Care also had blood pressure monitored using a Dinamap automatic blood pressure machine. This was interfaced into a BBC microcomputer for analysis as previously described (Chapter 2). Ten blood pressure readings were taken over a 10 minute period. Similar analysis to those above were carried out to see whether there was any trend from beginning to end and how many blood pressure readings were required using a Dinamap to give an average which would then no longer vary. The average of the Dinamap readings were then also compared with the average of the nurses' readings taken in Day Care.

Method

All the patients were sitting in a comfortable chair, the right arm was used for blood pressure measurement and care was taken to make sure that the cuff of the sphygmomanometer was at the level of the heart. The Dinamap used a diastolic which is automatically assessed by the machine which lies somewhere between Phase 4 and Phase 5. It was therefore expected that the Dinamap blood pressure recorder would produce results which were lower than those found by the nursing staff. The variation, however, should have been the same.

Results

As predicted the Dinamap readings were found to be on average 8 mmHg lower for diastolic blood pressure compared with the nurses readings (Fig 5.14). When the average of the first two Dinamap diastolic blood pressures were compared, there was a significant reduction (Fig. 5.15). but no difference following this. This might imply that the patients were initially anxious but the pulse rate showed a gradual rise over the first four readings (Fig 5.16). If anxiety was the cause of the change of blood pressure readings, the pulse rate would have been expected to fall, not rise.

The variation found between the first two readings is shown in figure 5.17.

If this is compared results from the nurse's readings (Fig 5.7), it can be seen that the degree of variation was similar.

When the end digit was studied, there was no obvious predominance found (Fig. 5.18). This is to be expected as there is no reason for the machine to favour any given result. When these results are compared to the results found with readings by the nursing staff (Fig, 5.8), no significant difference was found (Chi square test). This suggests that the nursing staff were taking reasonable care to read an accurate result.

When the serial averages were compared, there was little difference found after six readings were used (Fig.5.19). After this, a persistent average (a change of less than 5 mmHg) was achieved in 97% of the patients (Fig. 5.20). After 8 readings, this rose to

99%. The difference between this result and that found with the nurses readings is probably related to the fact that there is a significant fall in the first two blood pressure readings.

Discussion

The Dinamap appears to give similar findings to the previous studies. This suggests that the variation in blood pressure is on a minute to minute basis and is a genuine physiological finding and not due to human error. Averaging the Dinamap readings gives an accurate measurement of blood pressure range but the level of diastolic blood pressures appears to be lower when compared with the nurse's readings. This finding was expected as the Dinamap measures a diastolic blood pressure between Phase 4 and 5. There is no reason that the Dinamap blood pressure recorder could not be used for the assessment of hypertension but a lower cut off point for abnormality is probably required. An average of 8 readings would appear to give an accurate result in 99% of patients.

5.7 Discussion

The accurate diagnosis of hypertension is critical, as it is associated both with increased morbidity and mortality for mother and baby (Friedman and Neff, 1975; Friedman and Neff, 1976; Friedman and Neff, 1978). It is also a reason for a large percentage of antenatal admissions to hospital (Hall, Chang and MacGillivray, 1980). It is also important that if a patient is at risk, she should be monitored closely. On the other hand, overdiagnosis of hypertension is common and one of the reasons for this could be the variability of blood pressure in the normal pregnant patient.

These studies confirm the wide variation of blood pressure readings that occur on a minute to minute and hour to hour basis. This appears to be true irrespective of the blood pressure level although there is a trend towards the group mean. The repeated blood pressure reading may be higher or lower than the initial blood pressure reading. If the variation is as much as 15 mmHg, it means that patients with an average blood pressure in the low 80's could occasionally get a blood pressure reading of over 90. The more often that blood pressure is measured in a given patient, the more often she attends the outpatient clinics, the more likely she is to have a single hypertensive reading.

The idea that blood pressure will settle after a period of rest is not supported by this study. Although the Dinamap study showed a fall from the first reading to the next one taken 1 minute later, there is no obvious trend of blood pressure levels from high to low over repeated readings over time. In both the clinic and the Daycare study, blood pressure was equally likely to rise with the second reading as it was to fall. It is not surprising that if a blood pressure reading of 90 mmHg diastolic was repeated within 10 minutes that a lower blood pressure would be found but similarly it would

be possible if you repeated a blood pressure reading of 85 mmHg that a reading over 90 mmHg might be found. Therefore, any given blood pressure reading will be a sample of a range of blood pressures. The limits of this range may be as much as 15 mmHg above or below that reading. Two readings would improve on this, but an average should be taken, not the lower reading. There is no obvious sense of using the lowest blood pressure reading any more than of using the highest blood pressure reading. If repeated blood pressure readings are taken, an average of 4 would appear to give a reasonably accurate assessment of the 'true' blood pressure, with the confidence limits of around 98%.

If this method of blood pressure assessment is used, it may help to reduce the diagnosis of hypertension compared to a method using a single blood pressure reading. It may be found that 4 blood pressure readings over half an hour, resting in the clinic, and averaged , would reduce the need for the patient to attend Daycare or be admitted to hospital. This study was not designed to answer this question. Other workers have suggested that the use of automatic blood pressure recorders may do the same job (Mooney and Dalton, 1990). Care is needed to make sure that the machine is measuring the same as the midwife. The Dinamap study showed that although it could be used, a lower cut off point is required as the diastolic blood pressure found is lower than the phase four normally used.

Since there is so much variation in the blood pressure, it may be that blood pressure alone is not an accurate method of diagnosing preeclampsia. The addition of biochemical testing may well help to increase the accuracy of the diagnosis.

5.6 Conclusions.

The main conclusions from these studies are:

1) Blood pressure **variability is normal** and should not be seen as abnormal.
2) Blood pressure **does not settle** with rest over a few hours.
3) A **single blood pressure measurement should not be used** for management decisions.
4) A repeated measurement is not a more accurate result.
5) An **average blood pressure** of at least four readings should be used for diagnosis and management.
6) Single blood pressure readings can be used in group studies.
7) Since there is so much variation, it may be that **blood pressure alone is not an accurate** method of diagnosing preeclampsia and should be used as a screening test only.

CHAPTER 6

THE EVALUATION OF THE 'ROUTINE' INVESTIGATIONS USED IN THE ASSESSMENT OF PREGNANCY HYPERTENSION

6.1 Introduction

The diagnosis of preeclampsia is not straightforward. The primary sign of presentation is a rise in the blood pressure to a specific level. The studies in the previous chapter demonstrated that the blood pressure is variable and that no absolute measurement can be taken as the 'correct' one. This may explain why there is an overdiagnosis of the condition (Hall, Chang and MacGillivray, 1980). It is known that, in preeclampsia, various biochemical and haematological changes also occur (Redman, Beilin and Wilkinson, 1976; Redman, Bonnar and Beilin, 1978). These parameters could be used to help in the diagnosis of 'true' disease, and the monitoring of disease progression. If all parameters are normal, it would seem probable that the high blood pressure is transient in nature and is of less concern. If any are abnormal, it would suggest that the diagnosis is more likely to be preeclampsia. If there is a worsening of the values, it may predict the progression from moderate to severe disease.

The author considers that most obstetricians fail to make an accurate diagnosis in cases of pregnancy hypertension and tend to manage all cases as being in the same risk category. Once a diagnosis is made, there is often a failure to monitor the progressive nature of the disease in both the mother and fetus. To try to correct these deficiencies a stepwise approach to the management of hypertension in pregnancy was developed. The initial management was based on maternal monitoring. This concentrated on the changes found in blood pressure, renal function, including uric acid levels (Redman, Beilin and Wilkinson, 1976), liver function tests and haematological parameters, including platelet count (Redman, Bonnar and Beilin, 1978). Fetal monitoring consisted of cardiotocography and ultrasound. This chapter describes the results of these tests, their relationship to each other and to the pregnancy outcome.

6.2 Patient group

To study the relevance of these tests, 335 consecutive primigravida who had a diastolic blood pressure below 90 mmHg in the first trimester and presented after 24 weeks with a diastolic blood pressure persistently above 90 mmHg were reviewed (Table 6.1). None had a history of hypertension prior to pregnancy. These criteria were used in an attempt to select as 'pure' a group as possible for investigation. The relationship between the booking parameters, the parameters at the time of the hypertension and the measurements of pregnancy outcome were studied.

Statistics

As many of the changes seen in these parameters may be interdependent, it was decided to use multiple regression analysis to look for any independent relationships between the selected measurements. A stepdown procedure was used to

check the validity of the significant results. This involves the removal of the non-significant results in a stepwise fashion until only the significant results are left. For convenience, only the full results will be displayed with the significant values highlighted. This was carried out with the help of Dr Pravn of the University Department of Statistics at Glasgow University.

6.3 Booking parameters

The mean and range of the parameters studied are shown in table 6.1. Tables 6.2 and 6.3 show the results of multiple regression analysis which demonstrates evidence of an independent relationship between the parameters. The results show that systolic and diastolic blood pressures are closely related. There is also a relationship between maternal weight and both systolic and diastolic blood pressure. It would appear that a rise of 10 Kg in weight will change the blood pressure by 1 mmHg. This may appear to be a relatively small effect. However, at the extremes of weight the difference is more significant, 8 mmHg between weights of 40 Kg and 120 Kg. If the patient was heavier, a larger width blood pressure cuff was used. Therefore, it is felt that these differences are real. It is difficult to know whether these changes imply that the heavier patient is at increased risk because of this difference or less risk because the blood pressure is less elevated for them. There is no relationship with patient height, booking haemoglobin, haematocrit or blood pressure measurements. The Adjusted Coefficient (R^2) is only 0.4 for both the systolic and diastolic blood pressure suggesting that these particular parameters contribute to around 40% of the blood pressure changes.

Later parameters

The mean, standard deviation and range of the values obtained when the patients were hypertensive are seen in Table 6.4. The results used were either the last measurements carried out before delivery or before antihypertensive therapy was given, whichever was the later. Since, for each individual patient, they were taken at the same time point, they can be compared with each other. Although less accurate than creatinine as a measure of renal function, urea (Redman *et al.*, 1973) was used in the study as the creatinine values were not available for all patients. The birth weights were also converted into the birth centile for the delivery gestation in order to standardise the values. The following sections discuss the results of this analysis.

6.4 Blood Pressure

As already stated, although elevation of blood pressure constitutes the main maternal risk, it is very variable and may be a relatively inaccurate measure of disease severity. The average of four blood pressure readings taken in one day was used for these studies. Therefore, some patients had an average blood pressure of less than 90 mmHg (Table 6.4), although all were hypertensive with at least two

individual blood pressure readings over 90 mmHg on the day of assessment. All the other parameters show a wide range from well within the normal range to grossly abnormal.

Systolic Blood Pressure

Table 6.5 demonstrates the independent relationships with the systolic blood pressure. It is not surprising that there is a relationship with the booking blood pressure, but the effect is small. For every 10 mmHg change in the booking systolic, there is only a change of 2 mmHg in the last systolic. The only other results that are significant are the last haemoglobin and last haematocrit. The size of the coefficient depends on the actual value of the results. Therefore, the absolute value of the coefficient for haematocrit is considerably larger than that for haemoglobin because the absolute value of the haematocrit (e.g. 0.33) is usually around 35 times lower than that for the equivalent haemoglobin (11.5). The direction of effect is different for these parameters. This means that a higher systolic blood pressure is associated with a lower haemoglobin and a higher haematocrit. This implies the development of a relative macrocytic anaemia. This could be explained by chronic haemolysis (Weinstein, 1982) and a relative reticulocytosis. More studies are required into this as it could be an early sign of HELLP syndrome, an accepted serious complication of the condition (Weinstein, 1982). There is no correlation with any of the other disease markers such as urea, uric acid, and platelet count.

Diastolic Blood Pressure

Diastolic blood pressure is related to the booking diastolic but the coefficient is only 0.1 so the effect is even smaller than that for systolic blood pressure (Table 6.6). There is a significant independent relationship with the accepted markers of disease severity, urea (Redman *et al.*, 1973), uric acid (Redman, Beilin and Wilkinson, 1976) and platelet count (Redman, Bonnar and Beilin, 1978). There is also a significant relationship with haemoglobin. The direction of effect is opposite to that found with the systolic blood pressure implying that a rise in diastolic blood pressure is associated with a rise in haemoglobin.

Discussion

These results suggest that diastolic blood pressure and not the systolic appears to relate to the accepted parameters of disease severity such as uric acid and platelet count. This may imply that the rise in diastolic blood pressure is more relevant in pregnancy induced hypertension. This would be logical as the diastolic blood pressure is associated with the increased peripheral resistance seen in this condition. The factors that relate to rises in systolic blood pressure are different. Therefore, the rise in the systolic blood pressure may demonstrate a different aspect of the disease process. The changes seen with the haemoglobin and haematocrit are

confusing and require further study.

6.5 Studies of renal function.

Renal involvement is pathognomonic in preeclampsia and it is normally demonstrated by the presence of proteinuria (McCartney, 1964). There may be elevation of urea (Redman *et al.*, 1973) and creatinine (Zlatnik, Burmeister and Beach, 1982) as further evidence of impairment of renal function. Elevation of uric acid is associated with severe preeclampsia. Redman suggested that it was more closely correlated with fetal compromise than blood pressure (Redman, Beilin and Wilkinson, 1976). Uric acid is thought to correlate with renal tubular damage, but it may be elevated for reasons other than renal impairment alone (Beaufils *et al.*, 1981).

Urea

In this study creatinine was not available in all patients and was not used in the analysis. It is realised that urea is not as accurate as creatinine as a marker of renal impairment but an elevation of serum urea is suggestive of impaired renal function. In normal pregnancy, there is an increase in creatinine clearance leading to a fall in the serum urea. This means that the levels of urea found in pregnancy are approximately half those found in the non-pregnant. Very few of the patients studied had an abnormal level for pregnancy, suggesting that renal function is maintained in the majority of cases of pregnancy hypertension.

Multiple regression analysis shows that changes in urea relate independently to urate, Alt and booking haemoglobin (Table 6.7). Since the coefficients are small and the Adjusted Coefficient is only 0.3, changes in these parameters are only responsible for around 30% of the changes in urea. These results suggest that changes in renal function are relatively independent of the other changes in the disease parameters.

Uric Acid.

Uric acid is thought to correlate more closely with placental and fetal involvement than blood pressure (Redman, Beilin and Wilkinson, 1976). Multiple regression analysis shows that it is independently associated with diastolic blood pressure, Ast, serum albumin and urea (Table 6.8). This suggests that uric acid elevation is not only related to renal impairment but to some of the other systemic changes as well. These changes are related to cellular damage of the vascular endothelium and liver cells. Uric acid may be a marker of systemic involvement in preeclampsia rather than simply a marker of renal impairment. The rise in uric acid could be partly due to an increased production of urate associated with cellular damage. The relationship with renal function and tubular damage is not surprising since, when produced, urate is excreted by the renal tubule.

Proteinuria.

Proteinuria is associated with a higher incidence of fetal loss (Friedman and Neff, 1975). The majority of these patients did not have protein in the urine. Since so few babies are now lost, correlation of proteinuria with fetal survival is difficult to confirm.

Using multiple regression analysis, proteinuria was found to have a direct independent relationship only with albumin, and booking haemoglobin (Table 6.9). As would be expected, serum albumin was negatively related to urinary protein. There was no relationship between proteinuria and blood pressure or other parameters of disease severity, such as uric acid, urea or platelet count. This suggests that proteinuria is a specific marker of preeclampsia due to the presence of the renal lesion rather than a sign of disease 'severity'.

Discussion

The three 'renal' markers appear to have a degree of independence. The lesion associated with proteinuria is well recognised (McCartney, 1964) and is probably a specific primary lesion in the disease. It would appear to be independent of blood pressure level and is probably an absolute marker of the presence of 'true' preeclampsia. The absence of proteinuria does not mean that the patient does not have preeclampsia, but many of those without proteinuria will have a more benign form of hypertension. This could be partly explain why proteinuria is associated with a less successful outcome.

Although the changes in uric acid are most strongly related to signs of renal impairment, it also appears to be independently associated with changes of diastolic blood pressure, and the markers suggestive of liver function abnormality, Ast and serum Albumin. This suggests that the elevation in uric acid is at least partly related to signs of the systemic effects of the disease and may be a more accurate marker of progressive pregnancy induced hypertension than blood pressure alone. Renal impairment, as measured by urea, may or may not be present.

6.6 Haematological tests.

Haemoglobin

Haemolysis is recognised as a late, worrying sign in preeclampsia (Weinstein, 1982). There has been a suggestion that haemolysis may be an early sign in the development of the disease (Sarrel *et al.*, 1990). Multiple regression analysis shows the independent relationship of the last haemoglobin with the booking haemoglobin and haematocrit, the last haematocrit and the last blood pressure (Table 6.10). The direction of the association between the haemoglobin and the systolic blood pressure is negative but is positive with the diastolic blood pressure. This suggests that changes in the systolic and diastolic blood pressures are associated with

different effects on the haemoglobin levels.

Haematocrit

Multiple regression analysis shows an independent relationship with the booking haemoglobin and haematocrit, the last systolic, last haemoglobin and last albumin but not the last diastolic (Table 6.12). These associations appear to be in the opposite direction than those found with haemoglobin. This suggests that factors that reduce the haemoglobin will tend to increase the haematocrit. This can only result from a relative macrocytosis.

Platelets

Platelet consumption is thought to be an early abnormality in preeclampsia (Redman, Bonnar and Beilin, 1978). In the study group, the range of platelet counts was wide from 62 to 669 (Table 6.4). Platelet consumption is thought to relate to platelet and fibrin deposition in the placental and renal circulation. Multiple regression analysis demonstrated an independent relationship with booking weight, diastolic blood pressure, and Ast (Table 6.13). These results suggest that platelet consumption is linked to a diastolic rise rather than a rise in systolic blood pressure. However, since the Adjusted Coefficient (R^2) is only 0.2, these factors would appear to influence only 20% of the changes seen in platelet count.

Discussion

There appear to be few obvious relationships between haemoglobin, haematocrit and the other disease parameters. Where relationships are seen, the influences appear to have an opposite effect on haemoglobin compared to haematocrit. Low grade haemolysis could lead to a fall in haemoglobin and a rise in haematocrit due to a relative reticulocytosis. There are other influences such as haemoconcentration which would further complicate the relationships. These findings are confusing and require further study.

Changes in the platelet count are independently related to diastolic blood pressure and Ast. This suggests that the changes in platelet count are associated with damage to cell membranes and the liver mitochondria (Torbergsen *et al.*, 1989; Berkowitz *et al.*, 1990).

6.7 Combination of Blood Pressure, Uric Acid and Platelet Count.

As will be described fully in Chapter 7, the majority of the patients referred to the Daycare unit are found to be normotensive. Most of this group remained normotensive for the rest of their pregnancy, but some developed persistent, worsening hypertension. Since the purpose of Daycare is to screen out those who are and will remain normal, it is in the group that are normotensive at first visit that further tests of normality or abnormality will be potentially useful. If there were signs that signify increased risk, these patients could be monitored more closely.

Since blood pressure, uric acid levels and platelet count all appear to be associated with different aspects of the disease, it may be possible to use changes in these parameters as a method of diagnosis and assessment of risk. All three parameters were measured at the Daycare Assessment Unit (Chapter 7) and the predictive value of an individual result, or a combination of the three results, on the development of moderate to severe hypertension later in the pregnancy was studied. All these results were available on the day of attendance at Daycare.

One thousand and eighty seven consecutive primigravidae referred to the Daycare Unit because of elevation of blood pressure were studied. These patients attended between January 1985 and December 1989. The results obtained at the first daycare assessment were compared with the long term outcome of the pregnancy. The definitions of outcome, that were used, are listed in table 6.14.

Diastolic blood pressure alone

When the diastolic blood pressures were studied, it was found that 78% of the patients had an average pressure below 90 mmHg, 17% between 90-100 mmHg and the rest over 100 mmHg (Table 6.15). If the diastolic blood pressure was above 90 mmHg, no patient settled in the long term and 33% progressed to severe disease. Therefore, the average diastolic was an accurate method of diagnosing those patients with a persistent problem and at risk of progression.

Of the 846 patients with an average blood pressure below 90 mmHg, 86% remained either normal or mildly hypertensive for the rest of their pregnancy, while 13% developed moderate disease and 1% severe disease (Table 6.15).

Uric acid alone

Arbitrary values of normality and abnormality for uric acid were chosen. Only 14% of the patients had a uric acid of less than 250 umol/l, 72% between 250-370 umol/l and only 14% were in the highest abnormal range (Table 6.16). If the long term outcome is studied, there is a scatter of results in both the lower two ranges. This is not surprising since not all patients with an elevation of blood pressure will have an elevation of uric acid. However, if the uric acid was above 370 umol/l, all the patients developed at least moderate hypertension in their pregnancy (Table 6.16). As so few patients fell into this category, it was decided that, in future studies, 350 umol/l would be used as the cutoff point of normality.

Platelet count alone

When the platelet count was used, a count greater than $250x10^9$/ml was taken as completely normal, 150-$250x10^9$/ml as borderline and less than $150x10^9$/ml as abnormal. The majority of the patients had levels above $150x10^9$/ml with a scatter of outcomes (Table 6.17). This is not surprising since many of the hypertensive patients

will have normal platelet counts. All patients with a count less than $150x10^9$/ml developed hypertension of some degree during the rest of their pregnancy. Since using $150x10^9$/ml selected so few patients, a level of $200x10^9$/ml was used as the cutoff point of normality in future studies.

Combined results

Since these three parameters appear to be relatively independent, it was decided to study the effect of combining the results. Normal values were arbitrarily chosen as stated previously. The diastolic cutoff level of 'normality' was taken as 90 mmHg, the uric acid cutoff level as 350 umol/l and platelet count cutoff level as $200x10^9$/ml.

Diastolic Blood pressure alone

As already shown, 846 (78%) were assessed as normal (Table 6.18). Of these, only 293 (35%) remained completely normal, 434 (51%) developed mild disease which implies further blood pressures of 90 mmHg but no clinical problem. That left only 109 (13%) who developed moderate and 10 (1%) severe disease. Therefore, 78% of the attending patients were assessed as normal but 14% of these would progress to moderate or severe disease often requiring hospitalisation and treatment.

The addition of Uric Acid

If a uric acid of less than 350 umol/l was added to a normal blood pressure, 630 (58%) were classified as normal. In these patients, the predictability of the long term outcome of the pregnancies increased with 281 (45%) of the patients remaining normal, 276 (44%) becoming mildly hypertensive, 65 (10%) moderate and 8 (2%) progressing to the severe state (Table 6.18). This implies that 216 (26%) of the 846 patients were selected to be at higher risk because of an elevated uric acid. Of these, only 12 (5%) remained normal, 158 (73%) developed mild disease, 44 (20%) moderate and 2 (1%) severe disease. Therefore, a fewer number of patients are assessed to be low risk but the diagnosis is more accurate.

The addition of platelet count

If the first two parameters were associated with a platelet count greater than $200x10^9$/ml, 537 (49%) were diagnosed as normal. Of these, 264 (49%) remained normal, 245 (46%) mild, 22 (4%) moderate and 6 (1%) to severe disease. Therefore, a combination of these 3 parameters has a 95% predictive value of relative normality for the rest of the pregnancy.

This means that 83 (13%) of patients with normal diastolic blood pressure and normal uric acid were thought to be at risk because of a low platelet count. Of these patients 17 (20%) remained normal, 31 (37%) mild, 33 (40%) moderate and 2 (2%) became severe.

Discussion

It should be noted that the diagnosis of disease and severity was based on blood pressure with or without proteinuria. No attempt was made to verify the type of hypertension. It was felt that since it is the hypertension that normally triggers the change of management, that it should be the basis of diagnosis. What is clear from these results is that it is possible to improve the prediction of normality using tests which are simply done and assessed. It is also clear that the prediction is not absolute. Although there is an overall reduction of the selected patients progressing to moderate or severe disease, no matter what combination of tests are used, around 1-2% of the patients will develop severe disease. Therefore, even if the patients are assessed as normal, care should be taken as this does not exclude their progression to severe disease. Because of these findings, any patient assessed as normal is seen within 10 days of the Daycare appointment. This will be discussed more fully in Chapter 7.

6.8 Liver Function Tests.

Alkaline phosphatase, Alt, Ast and γGT are generally taken together as part of 'liver function tests'. This is largely inaccurate as they are elevated when liver cell damage or bile stasis occurs. Liver cell function is better assessed by measurement of bilirubin, albumin and a 'coagulation screen'. Therefore, abnormalities of these parameters are more likely to be associated with liver cellular damage which may also cause liver function problems. Abnormalities of liver enzymes are associated with severe disease (Weinstein, 1982). Abnormalities of liver pathology are found in fatal cases (Acosta Sison, 1931). Because of these accepted changes, various markers of liver abnormality were studied to see if they were related to the other parameters already discussed (Table 6.22).

Alkaline Phosphatase

Alkaline phosphatase is a series of isoenzymes which are present in liver, bone, kidney, placenta and intestinal mucosa. Levels are elevated in situations of bile stasis but various other factors also effect it. However, since it is present in abundance in liver cells, elevation in the serum is generally presumed to be caused by liver function abnormality. Multiple regression analysis demonstrates an independent relationship with γGT and albumin only (Table 6.19). The Adjusted Coefficient is only 0.2. Therefore, only around 20% of the changes in alkaline phosphatase can be explained by these parameters. This would suggest that changes in alkaline phosphatase cannot be used as a measure of disease activity as other factors are involved in alterations of its levels. This may be largely due to changes in placental alkaline phosphatase.

Alt and Ast

Alt is a cytosolic enzyme present in abundance in liver cells but is also present in the kidney, heart and skeletal muscle. Ast comes from the mitochondria of cells and is the mostly widely used marker of liver cell abnormality. It is also elevated in cases of myocardial infarction secondary to cardiac cell damage.

Multiple regression analysis shows the independent relationship of Alt with urea, Ast and γGT (Table 6.20). This suggests that the Alt rise may be partly due to renal impairment which could be explained by its known presence in renal tissue. A relationship was also seen with the booking haemoglobin.

Ast relates to urate, platelet count and Alt (Table 6.21). Ast appears to relate to the recognised markers of disease severity rather than the other liver parameters. Since Ast is a mitochondrial enzyme, a rise in Ast would appear to be more fundamental to cellular damage than the other liver markers. This is also the reason why Ast rises after myocardial infarction. Other signs of mitochondrial damage have been found in preeclampsia (Torbergsen *et al.*, 1989; Berkowitz *et al.*, 1990; Shanklin and Sibai, 1990).

γGT

γGT is commonly elevated in cirrhosis of the liver where there is damage to the liver cells. It can be seen as a non-specific sign of liver cell abnormality. However, apart from the relationship with booking height, it is independently related only to alkaline phosphatase and Alt (Table 6.22). As it is only related to the other factors of liver damage and not independently with anything else, γGT would appear to reflect liver involvement alone.

Albumin

Albumin is synthesised in the liver. Therefore, liver function abnormality may be reflected by lower serum albumin levels. In preeclampsia, proteinuria would also tend to result in lower levels of serum albumin. Multiple regression analysis shows that albumin has an independent relationship only with urate, Hct, alkaline phosphatase and proteinuria (Table 6.23). The relationship with Hct is positive, suggesting that this may be evidence of the haemoconcentration seen in worsening disease. The other relationships show that changes in albumin are linked to systemic changes in disease activity and not simply a loss of albumin from the kidney. The Adjusted Coefficient is only 0.3 suggesting only 30% of the changes in albumin can be explained by these changes. Therefore, the reason for serum albumin changes is multifactorial.

Discussion

It is clear that the different 'liver' parameters are affected by different things. Although, a rise in Ast is generally accompanied by rises in Alt and γGT, γGT appears

to be a 'purely' liver parameter, Alt related to renal function abnormality and Ast related to the systemic disease parameters.

Albumin is affected by a multitude of factors. Some will tend to increase the level and others reduce it. Low albumin will lead to increased interstitial fluid. In its most benign form this is oedema, but if severe, it could lead to pulmonary problems with respiratory embarrassment. This is now an increasing cause of maternal mortality and morbidity. The causes of low albumin would be a useful area of further research.

6.9 Outcome parameters

It would be useful if simple blood tests could correlate well with the outcome of the pregnancy. Three main outcome parameters were studied, the gestation of delivery, the birth weight and centile and the Apgar score.

Delivery Gestation

Delivery gestation is a parameter of significant importance. Epidemiology studies demonstrate that fetal survival at earlier gestations are greatly reduced (Friedman and Neff, 1975). Factors that influence the gestation at delivery, will, therefore, influence the survival of the fetus.

There was an independent relationship between delivery gestation and urea, platelets, and proteinuria only (Table 6.25). During the time of this study, the presence of proteinuria was not used as a sole criteria for delivery. This suggests that earlier gestation of delivery is associated with the presence of proteinuria, renal impairment, as marked by elevated serum urea, and platelet consumption. The reasons for this could be multiple but it does suggest that the earlier the disease presents, the more severe it appears to be with the presence of proteinuria and a low platelet count. Studies presented in Chapter 8 also show that platelet numbers were lower in patients presenting earlier in pregnancy.

Birth weight

The birth weight of the baby is dependent on the placental function and the gestation at delivery. To counteract the effect of gestation, the birth centile was also calculated based on normal figures for Scotland.

There was an independent relationship with the mother's booking height and weight, urea, alkaline phosphatase , albumin and delivery gestation but not blood pressure (Table 6.26). It is interesting to note that the weight increased on average by 171.3 gms per week. If the weight centile is studied, there was an independent relationship with booking haemoglobin and haematocrit, delivery gestation and birth weight (Table 6.27). Since the relationship with gestation is negative, it would appear that growth retardation is more likely at later gestations. There do not appear to be any other parameters that relate to weight centile apart from booking haematology. This would imply that it is the length of time the disease is present that

influences the weight centile, not disease severity itself.

Apgar score

Assessment of the fetus at delivery is based on the Apgar score despite its recognised limitations. There was an independent relationship between the one minute score and urea, delivery gestation, birth weight and weight centile (Table 6.28). The five minute scores are related to the systolic pressure and the one minute score only (Table 6.29). These results suggest that the state of the baby at birth is mostly related to gestation and weight of the baby rather than the disease severity.

6.10 Tests of Fetal Wellbeing

Over the years, various tests of fetal wellbeing have been employed. In 1980, the main tests used were the biochemical 'placental function' tests, human placental lactogen and estriol. For a number of reasons, these were not thought to be immediate enough and more direct tests of fetal wellbeing were sought. Over the time of the study, the main test used was the cardiotocograph with 'descriptive' ultrasound estimations of fetal weight and liquor volume. Doppler ultrasound of both maternal and fetal vessels have been added more recently.

In most of the hypertensive patients, the babies did well. A close evaluation of 186 proteinuric primigravidae was carried out and the results of monitoring tests were correlated with fetal outcome. These patients were those managed between January 1981 and December 1989. They include all those where full monitoring was carried out before delivery. The results used were the last carried out before delivery. S/D ratio is the ratio of the systolic and diastolic Doppler flow velocity measurement in the assessed blood vessel. This parameter is an measurement independent of the angle of the Doppler transducer to the vessel being investigated. It widely used in maternal/fetal assessment (Fitzgerald and Drumm, 1977; Campbell *et al.*, 1983; Cameron *et al.*, 1988). Abnormalities are thought to relate to diminished fetal/maternal blood flow leading to fetal compromise.

Of the 186 patients, 57 presented before 30 weeks and 129 presented in or after the 30 th week (Table 6.30). These two groups were compared. None of the parameters relating to maternal disease, except proteinuria, showed any significant difference. These findings confirm the finding that proteinuria is independently related to the gestation at delivery. All the parameters of fetal wellbeing showed a significant difference between those presenting below and after 30 weeks. There was a higher incidence of abnormal markers of fetal wellbeing seen in the earlier group. This suggests that the earlier the presentation, the worse the fetal condition. Of the 129 pregnancies presenting after 30 weeks, 123 (95%) resulted in a surviving baby compared with only 36 out of 57 (63%) presenting prior to 30 weeks. It would appear that this was partly because of prematurity and partly because those presenting at an

earlier gestation showed evidence of increased fetal compromise.

If only those pregnancies that presented before 30 weeks are studied (Table 6.31), it can be seen that fetal survival is associated with satisfactory signs of fetal wellbeing, such as a reactive cardiotocograph, normal Doppler ultrasound and good fetal growth. Traditional tests of disease severity, including proteinuria, did not correlate with fetal survival. If pregnancies could be prolonged until after thirty weeks, the survival was better, as would be expected. A reactive cardiotocograph would appear to be the best predictive test for fetal survival. However, even a decelerative tracing is associated with a surviving fetus in over 60% of cases and there was no significant difference in this respect between the survivors and those that died. Similarly, normal Doppler results were also associated with a good fetal outcome. Normal amniotic fluid volume was associated with a better outcome. If growth retardation was present or if delivery was due to fetal compromise, the incidence of fetal loss was significantly higher.

Discussion

These results suggest that markers of maternal disease do not influence the perinatal outcome. If proteinuria is present, the **level** of proteinuria does not influence the fetal outcome. This would support the idea that the presence of proteinuria marks 'true' preeclampsia, and, therefore, increased risk. The risk does not increase with the level of protein. The most important parameter as far as the fetus is concerned is the gestation at presentation. After 30 weeks, the fetus almost always survives. This is probably due to the fact that delivery is possible but also that the fetus would appear to be in better condition if the presentation is after 30 weeks. It is obvious that signs of fetal compromise increase the chances of fetal loss, but it is not inevitable. Even in the presence of a premature, growth retarded fetus with abnormal CTG or Doppler, fetal loss is not certain and the fetus should not be 'written off'.

6.11 Discussion

These results confirm that preeclampsia is a systemic disease and effects can be seen even in the mild to moderate patients. Abnormalities of liver enzymes are not present only in the severely affected group. The liver abnormalities are affected by different influences. Ast may be the most sensitive marker of liver cell involvement. Uric acid levels appear to be related most closely to urea but also to the other 'systemic' markers of diastolic blood pressure, albumin and Ast. Therefore, uric acid is related to other signs suggestive of cellular damage. These changes may be present even in the milder forms of the disease. The severe signs of HELLP syndrome may simply be a continuum and not a different disease entity (Greer, Cameron and Walker, 1985). The changes seen in haemoglobin and haematocrit could be due to chronic haemolysis but there is no direct evidence of this and further studies are required.

The renal involvement is not due purely to the glomerular lesion as the changes in uric acid and Alt suggest the possibility of fundamental cellular damage, particularly in the tubules.

It is clear that low albumin is due to a multitude of factors including liver cell damage and proteinuria. There are conflicting influences on it, with Hct positively related demonstrating the effect of haemoconcentration and increasing proteinuria tending to produce a reduction in serum albumin.

Proteinuria does not relate to any other disease parameter and is probably not a sign of 'severity' but confirmation of the 'true' diagnosis. It is related to the gestation of delivery, suggesting that it is more often present when the patient presents at earlier gestation.

Therefore, this is a multisystem disease and in any given patient different systems are affected to different degrees. It would appear that by using diastolic blood pressure, uric acid and platelet count most areas of potential disease involvement are being investigated. Using these three parameters for maternal monitoring, it is possible to improve the differentiation of normality from abnormality. However, it is not absolute and some patients will progress to more severe disease without clear early signs. The parameters would appear to be better at predicting progression to moderate than to severe disease.

The fact that the outcome for the fetus appears to be independent of the maternal disease state, accentuates the need for the fetus to be monitored separately. In the presence of satisfactory tests of fetal wellbeing, the fetus can do well even in the presence of severe maternal disease. This may allow aggressive antihypertensive therapy to prolong pregnancies. If the pregnancy is prolonged beyond 30 weeks, the outcome is improved. Although this may be due to the prolongation of the pregnancy, it may be due purely to the fact that the fetus is in good enough condition to allow continuation of the pregnancy, so increasing the chance of survival.

The condition of the baby at birth is related to the delivery gestation and birth weight. The only maternal parameter which appears to affect it is urea and possibly systolic blood pressure. This is difficult to explain unless urea is raised only in severe disease. However urea appears relatively independent of disease severity. It is possible that diminished renal function is responsible for suppression of the fetus at birth because of an increase of a 'toxic' substance.

Birth weight was related to booking height and weight which is not surprising but the relationship is lost when centiles are used. The centile is related to the booking haemoglobin and haematocrit. This suggests that the fitness of the mother and her adaption to her pregnancy will effect the outcome for the baby. It is already known that a booking weight of less than 50 Kg increases the chances of low birth weight and

other pregnancy complications. Birth weight was affected by the level of albumin in a negative way; the lower the albumin the higher the birth weight. Low albumin is known to be related to maternal oedema. Oedema is associated with larger babies (MacGillivray and Campbell, 1980). The larger baby weight may be due to increased fetal fluid because of reduced maternal osmolality due to low albumin. There was no recording of oedema in this study. This finding is lost when looking at birth centile. This is strange as albumin does not appear to be related to gestation at delivery.

It was disappointing that booking parameters were not clearly related to development of the disease. It was hoped that the studies would suggest a potential screening test for the risk of pregnancy hypertension. However this is a selected group who had all developed a degree of hypertension and the results cannot exclude an association between booking parameters and preeclampsia in an unselected group of normal booking patients. Booking haemoglobin and haematocrit do relate to birth centile, which suggests an interesting area of further study.

6.12 Conclusions

The main conclusions in this chapter are:

1) Preeclampsia is a **systemic disease** with evidence of multiple organ involvement.
2) **Diastolic blood pressure, uric acid and platelets** can be used to monitor patients successfully and can be used as **predictors** of outcome.
3) Proteinuria is due to a **specific renal lesion** and is not associated with other disease parameters. It is probably a marker of **true** disease.
4) Albumin levels are effected by **multiple factors** and are not simply related to renal loss.
5) **Liver abnormalities are common** at all stages of disease severity.
6) The fetus requires **specific monitoring** as its problems are not predicted by maternal disease parameters.
7) The **gestation at clinical onset** is the most relevant parameter for fetal outcome.
8) **Growth retardation** is associated with disease presentation at a **later gestation.**

CHAPTER 7

THE DAYCARE ASSESSMENT UNIT

7.1 Introduction

As already stated, hypertension is a common problem of pregnancy and occurs in between 12 and 15 % of pregnancies (Scottish Home And Health Department, 1989; Chamberlain *et al.*, 1978b) and is associated with increased risk both to the mother and the fetus (Kirshon *et al.*, 1990; Page and Christianson, 1976; Turnbull, 1987; Turnbull *et al.*, 1989). When found to be hypertensive, most patients are admitted for observation and bed rest. (Chamberlain *et al.*, 1978a; Trudinger and Parik, 1982). This management dates from the 1950's (Hamlin, 1952) and has led to approximately 25% of all antenatal admissions being due to hypertension. Overdiagnosis is common and over 50% of patients admitted as hypertensive are found to be normotensive on admission (Hall, Chang and MacGillivray, 1980).

Despite this policy, maternal and perinatal mortality from hypertension in pregnancy did not change over a twenty year period (Turnbull, 1987; Turnbull *et al.*, 1989). However, the majority of patients do well, with the maternal mortality from hypertension being 1/11000 in Scotland and the perinatal mortality related to hypertension being 12/1000 hypertensive pregnancies, which is not much greater than the national average of 10.2/1000 (Scottish Home And Health Department, 1989). The routine admission of patients with hypertension has been challenged (Matthews, Patel and Sengupta, 1971) as there appears to be no evidence to show that bed rest is of benefit (Matthews, 1977; Crowther and Chalmers, 1989). However, it is accepted that there is a need to monitor the pregnancies closely.

Chapter 5 demonstrated that blood pressure is very variable and the diagnosis may be inaccurate. There may not be a need to admit all patients, but further assessment is probably required. This has led to the concept of developing an inpatient monitoring system delivered on an outpatient basis. The aim of the project was to develop an outpatient daycare management system where the degree of the blood pressure problem could be assessed and the need for admission decided. The unit would act as a filter for the need for hospital admission. It was predicted that the system would increase the access to full monitoring but reduce the number of admissions. This would allow the targeting of in-patient care to the patients who would most benefit from it.

7.2 Methods

Patients selection

The aim was to monitor all patients thought to be at risk of a hypertensive problem. No firm guidelines for patient selection were issued as it was felt that each obstetrician would have different criteria of risk. General guidelines of risk factors were given and the reasons for referral are listed in Table 7.1. The consultant obstetrician was free either to refer the patient to daycare or admit to hospital as he

saw fit. Patients referred from the antenatal clinic were seen in day care either on the same day or on a day suitable to the patient within the next four days.

This project was started in the summer of 1981 before the analysis described in the previous chapters. Therefore the protocols did not take into account the findings previously described.

Investigations

A protocol was developed to provide full monitoring for the mother and for assessment of fetal wellbeing (Table 7.2). The patient attended between 9.00 and 9.30 in the morning. Venesection was performed and a blood sample taken (Table 7.2). The urine was tested for presence of protein. As blood pressure was known to vary, it was decided to use five blood pressure readings taken over three hours. Surveillance of fetal wellbeing was made by subjective assessment of fetal movements and cardiotocograph over 40 minutes. Ultrasound examination for fetal weight estimation (Jeanty *et al.*, 1984) and liquor volume was performed if fetal growth deficiency was suspected and in those patients referred for a second time with moderate hypertension. Since August 1984, all data was collected and entered into a BBC microcomputer using specially designed software (Chapter 2). This has provided continuing audit and greater ability to analyse the data.

Patient assessment

All results were available by 12.30 pm and displayed on the computer screen (Fig 2.3). The patient was then interviewed and further management was discussed. Although the referring consultant was able to assess the patient if he wished, most of the assessments were carried out by the attendant medical staff. During the early years of this study this assessment was carried out by the author, but, latterly, help in running the unit was provided by a specially trained registrar. Patients were classified as being of normal/low risk, mild/moderate risk or of high risk of blood pressure problems using the 4 main parameters: blood pressure (average of 5 readings), platelet count (Redman, Bonnar and Beilin, 1978), uric acid (Redman, Beilin and Wilkinson, 1976) and urinalysis (Friedman and Neff, 1975) (Table 7.3). The results of the assessment of fetal wellbeing was also taken into consideration regarding further management. A normal cardiotocograph was taken as one with four accelerations within the 40 minute period, beat to beat variation of at least 20 bpm and the absence of decelerations.

The choices of management were based on these three risk categories provided fetal well being was confirmed by cardiotocograph and/or ultrasound. If normal or low risk the patient was referred back to the antenatal clinic. This return appointment must be within 10 days of their Daycare appointment. If moderate risk, the patient was brought back for a return visit at the day care unit, either the same or the

following week to assess any progress of the disease. If the risk was high, the patient was admitted to hospital the same day or the next when further observation and management would be carried out. At all times, the system allowed flexibility to overrule the protocol and bring the patient back to daycare or to admit them to hospital if there was any doubt about the safety of the mother or the fetus.

Since computerisation of the data, a full display of the patients previous attendances and assessment of any change in the parameters has been possible (Fig. 2.3). A printed copy of the results was inserted in the case notes and the consultant received a summary of all the attendances of their patients each week.

Facilities

The unit initially used the day area of one of the antenatal wards and then gradually took over a larger area. It is presently housed in a ward area adjacent to the ultrasound department. It comprises 3 separate rooms; a sitting area where patients stay most of the time, a centre room for the nursing station, computer centre and 2 cubicles for counselling. The third area is used for monitoring with 4 beds, each with a cardiotocograph monitor.

The unit has been open for 5 days a week from 8 a.m. until 5 p.m. since August 1981. Initially, the antenatal ward staff ran the unit. From 1983 a dedicated midwifery sister was allocated and the present staffing level comprises 2 midwifery sisters, a staff midwife and a student midwife. The need for this level of nursing staff had become necessary because of the increasing utilisation of Daycare for other areas of high risk antenatal monitoring.

Assessment of the effect of Daycare

All patients who attended Daycare were followed up until delivery and the outcome noted. Hospital admissions, numbers and diagnoses were obtained from the hospital records department and from the Information Services Department of the Scottish Home and Health Department. Antenatal inpatient nights were counted for every April and averaged as confirmation of the reduction of antenatal bed occupancy. Statistical comparisons of the changes seen were carried out using Fishers exact test.

7.3 Results

Number of referrals

Daycare first started in a small way with referrals from 2 consultant units in August 1981. Only 25 patients were seen before the end of the first year. The number of attendances has steadily risen and by the end of 1989 a total of 3156 patients had attended (Table 7.4). Most patients seen were primigravida (1641). The diagnosis at time of referral was mostly pregnancy induced hypertension (2793) but 221 had essential hypertension and 142 were seen because of past history and were normal at the time of referral. The average gestation at referral was 33±6 weeks and most

patients (1925) were between 32 and 40 weeks. However, 568 presented before 28 and 190 after 40 weeks. Most referral diastolic blood pressures (DBP) were between 90 and 100 diastolic (68%) but 5% of the referrals had a DBP above 110 mmHg (Table 7.5). The average DBP found at Daycare was 10 mmHg lower than the referral DBP and the majority of the patients had an average DBP of below 90 mmHg. Of the patients with referral DBP of over 90 mmHg only 25% came under the same category at Daycare assessment (Table 7.5). The Daycare Unit was primarily an assessment unit, and the majority of the patients were seen only once (62.4%) (Fig 7.1). However, the average number of visits was 2.1±0.7 and 461 patients had more than 3 visits. If continuous Daycare was used, no patient was seen more than twice in one week. If the patient was thought to require more frequent attendances, she was admitted to hospital.

At the first Daycare attendance, patients were grouped into 3 risk categories (Table 7.3) with the majority of patients being assessed as normal or low risk (Table 7.6). Overall, 67.9% were referred back to antenatal clinic and only 4% were admitted to the antenatal ward (Fig 7.1). The assessment at Daycare appeared to be accurate in the majority of patients but 26% of those referred back to the antenatal clinic returned to daycare at a later date. Overall 16% of the patients eventually required admission but this was delayed in around 75% of cases (Table 7.6) Therefore, of patients referred back to the antenatal clinic a significant number developed worsening hypertension highlighting the need for continuing vigilance and the need to reassess risk factors. No patient who was assessed as high risk reduced their risk at a later date.

Maternal Outcome

Three patients developed severe hypertension with symptoms prior to their next appointment, one of whom had failed to return for follow-up. Apart from these events, all patients did well and there were no cases of maternal death or eclampsia.

Fetal Outcome

The outcome of all pregnancies is given in Table 7.6. Overall perinatal mortality was 3.5/1000. The outcome was worse in patients admitted compared to those managed as outpatients due to the selection of severity. There were three perinatal deaths in the outpatients group (no admission at all = Return to Antenatal clinic + Return to Daycare). One patient was seen on a Friday, was of moderate risk, but returned after the weekend with an intrauterine death. Another perinatal death was due to a placental abruption and the third due to a congenital heart defect. The overall perinatal mortality rate was 1.1/1000 for the 2650 patients managed totally as outpatients.

The effect of Daycare

Over the last five years all consultants in the hospital have utilised the service and

the numbers have remained constant. Since 1985, the average number of Daycare referrals was 113/1000 deliveries (Table 7.4). The percentage of patients, who were diagnosed as hypertensive, changed little over the study period but the total number of patients monitored (daycare + admission) has risen (Fig. 7.2). Although some patients come into both categories, this would imply that a greater percentage (85%) are monitored in 1988-89 compared with 1980-81 (62%) ($P<0.0001$). The most significant change has been in the number of inpatient days due to hypertension. In the years 1980-81 there were over 2000 inpatient days as compared to under 750 for 1988-89. This is a highly significant reduction of 70% ($p<0.0001$).

The average antenatal bed occupancy for April for the year 1981 was 57/night and this had fallen to 20/night in 1989 ($p<0.0001$). This is not purely due to a reduction in the admission of hypertensive patients but also the increasing use of Daycare for all high risk monitoring.

A comparison with the 4 other large maternity hospitals in Central Scotland which did not have a Daycare Unit is shown in Table 7.7. These hospitals were chosen as those being nearest the Glasgow Royal Maternity Hospital and delivering around the same number of patients. The figures are for 1986 and 1987 and are taken from the Information Services Department of the Scottish Home and Health Department (Rosenberg and Twaddle, 1990). There is wide variation between the hospitals but the Glasgow Royal Maternity Hospital had fewer admissions and inpatient days per 1000 deliveries than any of the other hospitals. The size of the difference ranged from 41% to over 60%.

7.4 Discussion

As a common disorder, hypertension has been a burden on the health services resources in terms of manpower and hospital accommodation (Hall, Chang and MacGillivray, 1980) The high prevalence of the condition with its potential harmful effects for the mother and baby, makes it a difficult management problem for the obstetrician.

Pregnancy hypertension is thought to be unpredictable and most obstetricians would admit the hypertensive patient for closer monitoring of both mother and baby (Chamberlain *et al.*, 1978a; Trudinger and Parik, 1982), This "play safe approach" can cause much inconvenience to the patient and her existing family (Hall, Chang and MacGillivray, 1980). Mild to moderate disease carries little risk unless there is progression to the more severe form (Collins and Wallenburg, 1989). Therefore, the majority of the patients can be safely managed at home if there is access to adequate fetal and maternal monitoring. The idea of outpatient management is not new (Matthews, Patel and Sengupta, 1971), and Matthews showed that in the absence of proteinuria, non-admission to hospital had no detrimental effect on the

hypertensive patient (Matthews, 1977). Inpatient management may vary between different hospitals but the cornerstone is to keep the patient in to allow serial monitoring of blood pressure. Strict bedrest has been suggested as having therapeutic value but never been substantiated (Crowther and Chalmers, 1989) As some of these patients will progress to more severe forms of the disease, it is important that there is early recognition of any signs of progression (Collins and Wallenburg, 1989)

Daycare was envisaged as a system of reducing admissions to the hospital by providing a third option of antenatal care for the 'at risk' patient. The aim was to provide **inpatient monitoring facilities on an outpatient basis**. This would allow an increased access to monitoring for all the hypertensive patients.

Other forms of monitoring have become available that allows closer monitoring of the fetus to be carried out on an outpatient basis. Home cardiotocography (Dawson *et al.*, 1989), district midwives measuring blood pressure at home (Willis and Sharp, 1982) and home blood pressure monitoring using battery sphygmomanometers (Dawson, Middlemiss and Vanner, 1989) have all been advocated. All these methods do not use adjunctive biochemical and haematological investigations that are normally available in the hospital setting. Studies have shown the predictive value of platelet count (Redman, Bonnar and Beilin, 1978) and uric acid (Redman, Beilin and Wilkinson, 1976) estimations for the assessment of ongoing risk. The protocol that was developed used all the facilities that can be used for inpatient management and made them available for outpatients. As previously discussed in Chapter 5, blood pressure has an inherent variation (Murnaghan, 1987; Redman, Beilin and Bonnar, 1977a). The unit was set up before the results from Chapter 5 were available. Therefore, it was decided that five blood pressure readings were to be taken and averaged to try and overcome the problems of variation.

Daycare has developed rapidly due to the management flexibility it offers and the increasing faith that has developed among consultants in the hospital. This is reflected by the steadily increasing number of referrals. A greater percentage of the hypertensive patients are now fully monitored. There has been a fall in hypertensive admissions by nearly 70%. This has allowed a targeting of inpatient care to those requiring intensive monitoring and treatment. There is no evidence that the mothers or babies have suffered from non-admissions after introduction of the Daycare system.

The advantage of Daycare is that more than two thirds of the patients were diagnosed as normal and were returned back to the routine antenatal system after the first visit. Follow up of the patients shows that there is a chance that the patient may develop worsening hypertension. In those with increased risk of this, Daycare also allows continuous close monitoring as an outpatient.

Initially, all the patients were assessed by the main author but more recently, other members of staff have been trained in Daycare management. We have found that it is important to provide relatively senior medical cover for Daycare to make sure that there is adequate surveillance of the patients. This is important, not only for patient safety, but for the confidence of the consultants in the hospital. This confidence was successfully built up, after some initial resistance, when the benefits of Daycare were appreciated by both doctor and patient.

Daycare units are now well established in Scotland, with over 50% of the hospitals now having a designated daycare area (Rosenberg and Twaddle, 1990) The use of these areas varies widely. In the Glasgow Royal Maternity Hospital, all forms of intensive monitoring are now offered as an outpatient. This has helped to further reduce the inpatient load. The Unit also provides facilities for other specialist clinics such as diabetic, twin, epileptic, recurrent miscarriage, prepregnancy, and prenatal diagnosis.

Three problems remain before Daycare can be recommended as the main method of management of the 'at risk' antenatal patient.

Is it safe?

This was not a controlled trial. Daycare evolved out of a desire to improve the monitoring and diagnosis of hypertensive patients. Many obstetricians were wary of allowing patients home with a diastolic above 90 mmHg. A controlled trial has been carried out in Leeds but it is too small to show evidence on safety. Since, in the GRMH study, there were only 11 perinatal deaths in 3156 patients, it would be difficult to show that admission to hospital is any safer for the mother or baby or that Daycare was more dangerous.

Is it cost effective?

With nearly 70% reduction in inpatients days one would predict considerable saving on running costs. This, however, is difficult to prove. The hospital still needs most of the midwifery staff as it delivers the same number of patients. The most significant saving would be on capital cost when designing a new maternity hospital with a purposely built daycare facility or for larger number of deliveries to be managed through the existing facilities. A cost comparison study has been carried out between The Glasgow Royal Maternity Hospital and Aberdeen Maternity Hospital which uses Domiciliary Midwifes to check the patient's blood pressure at home. The results are not fully analysed but initial assessment suggests that Glasgow is cheaper on a patient cost basis (Rosenberg and Twaddle, 1990). There is a suggestion that a Daycare unit may increase the overall hospital workload despite reducing admission days. This was found in a study of before and after the introduction of a Pregnancy Assessment Day Unit in the Queen Mothers Hospital in Glasgow (Rosenberg and

Twaddle, 1990).

Are all these tests necessary?

The Daycare Unit was set up to provide blanket monitoring to make sure that the system did not miss any potential problem. It became obvious that many of the patients could have been diagnosed of being at low risk without many of the adjunctive tests. The problem is that it was not possible to know which patients would fall into this category prior to the daycare appointment. It is hoped to use the daycare experience to develop the optimal protocols for the management of all high risk pregnancy.

7.5 Conclusions

The main conclusions from this chapter were:

1) The majority of referred patients were **not found to be truly hypertensive.**
2) Most patients can be safely **managed as outpatients** with supportive outpatient monitoring.
3) Hospital **admissions can be reduced.**
4 The **outcome can be predicted** using tests outlined in Chapter 6.
5) To run a Daycare probably, dedicated trained medical staff are required.

Chapter 8

Changes in Platelet Size in Normal and Hypertensive Pregnancy

8.1 Introduction

The measurement of platelet size has been greatly facilitated by the generation of mean platelet volume (MPV) and a size distribution parameter (platelet distribution width; PDW) by the latest automated haematology laboratory equipment.

Platelet studies in pregnancy have, to date, yielded conflicting results. Giles (1981) reported no alteration in platelet numbers or MPV in 1087 normal pregnant women compared to non-pregnant controls and Harrison, Bramich & Collins (1982) also found no change in the platelet count in normal pregnancy. In contrast Hsieh & Cauchi (1983) reported a fall in the MPV in normal pregnancy, most profound in the first trimester but sustained throughout normal pregnancy. Meanwhile Fay, Hughes & Farron (1983) have reported a significant drop in platelet numbers in the last 8 weeks associated with a rise in the MPV in the last 4 weeks of normal gestation, and Sill, Lind & Walker (1985) have more recently reported increased MPV and PDW values between 34 and 37 weeks.

Many studies in women with pregnancy-induced hypertension (PIH) and preeclampsia have reported changes in platelet numbers, platelet survival and MPV which have been interpreted as evidence of increased platelet consumption (Redman, Bonnar and Beilin, 1978; Wallenburg and Rotmans, 1980; Giles, 1981; Giles and Inglis, 1981; Hsieh and Cauchi, 1983). However, since a decrease in platelet count is not inevitable, even at the onset of an eclamptic episode (Pritchard, Cunningham and Mason, 1976), it may be possible to show increasing platelet consumption in these patients by demonstrating an increase in platelet size, even though the platelet count remains within the normal range. Also, since Redman suggests that the fall in platelet count occurs before the rise in serum urate (Redman, Bonnar and Beilin, 1978), a change in mean platelet volume occurring prior to the fall in platelet count, may predict the progression of preeclampsia before it is clinically apparent.

These studies were to determine which (if any) of the reported platelet changes occur in normal pregnancy and abnormal pregnancy, with a view to the evaluation of the MPV as a parameter to identify women at risk of preeclampsia.

8.2 Patients and methods

Cross-sectional studies

Group A:- A control group of 20 non-pregnant females of similar age to the pregnant groups were studied.

Group b:- Blood samples from 208 healthy pregnant women were obtained during routine antenatal clinic attendances for a cross-sectional of normal pregnancy.

Group C:- Forty women with normal antenatal histories were studied sequentially in the third trimester, early labour and on day 5 postpartum. Twenty of these were also sampled 6 weeks postpartum. (Table 8.1)

Prospective studies

Four prospective studies on the predictive value of platelet size was carried out.

Group D:- Three hundred primigravid patients were studied between 28 and 30 weeks. A single blood sample was taken and the results obtained from these patients were compared with the outcome of their pregnancies.

Group E:- Samples were also obtained from 141 patients with pregnancy-induced hypertension (PIH).

Group F:- Forty patients with moderate PIH were followed serially from the gestation that the condition was first diagnosed. None of these patients were on any form of antihypertensive therapy when first selected for this study.

Group G:- Thirty-four patients with essential hypertension were followed from 24 weeks with serial blood sampling to study changes in platelet size. (Table 8.2)

Definitions used

In the studies of disease development or progression, mild PIH was defined as a persistent diastolic blood pressure greater than or equal to 90 mmHg, moderate PIH was defined as a persistent diastolic blood pressure greater than or equal to 100 mmHg. Severe PIH (preeclampsia) was defined as a persistent diastolic blood pressure of greater than or equal to 110 mmHg. Proteinuria was not used in the disease classification but was present in most cases of moderate and severe disease.

8.3 Sample handling

Blood samples were obtained from a large vein using a syringe and 19 G needle but no tourniquet. Blood was immediately mixed with K_2EDTA (1.5 mg/ml blood) and maintained at room temperature for 90-120 min. before analysis. Previous studies have demonstrated a time dependent change in platelet volume with a relative plateau between 60 and 150 min. after sampling (Rowan and Fraser, 1991). Analysis was carried out on a Coulter Counter Model S-Plus (Coulter Electronics Ltd., Luton, Beds, UK) which was subject to continuous quality control. Channel calibration with latex particles (Platelet Volume Calibration Latex, modal volume 8.6 fl; Coulter Electronics Ltd.) was carried out initially daily and later weekly to ensure sample comparability with respect to MPV and PDW values generated.

8.4 Results

Cross-sectional Study (Groups A&B)

The platelet count was unchanged throughout normal pregnancy when compared to non-pregnant controls (Table 8.3). However, both MPV ($p < 0.05$) and PDW ($p < 0.001$) increased in the third trimester. The increase in the MPV occurred after 34 weeks gestation ($p < 0.05$) whilst the PDW appears to increase throughout the third trimester ($p < 0.05$).

Serial Study of normal pregnancy (Group C)

Serial examination of forty healthy women from the third trimester to the puerperium (Table 8.4) revealed a similar increase in MPV ($p < 0.05$) and PDW ($p < 0.05$) in early labour and a striking fall in the MPV ($p < 0.005$) on the fifth postpartum day accompanying a rise in the platelet count ($p < 0.005$) and a fall in the PDW ($p < 0.005$). At the sixth post-natal week, the platelet count, MPV and PDW had returned to non- pregnant levels.

Prospective Primigravid Study (Group D)

Of the 300 normal primigravid pregnancies, 216 patients had no hypertensive problems throughout the rest of their pregnancy and 84 developed hypertension. When all parameters for these patients were compared, although a trend upwards could be seen, there was no significant difference found in any of the parameters measured (Table 8.5). However, if the MPV of this group was split into those who had a value above the mean and those below the mean, it can be seen that nearly all the patients who developed severe preeclampsia had MPV greater than the mean for the population at 28 and 30 weeks. (Table 8.6). Only one of the patients, who had a MPV below the mean, went on to develop severe preeclampsia, although others did go on and develop mild or moderate disease. This gives a high sensitivity of 88.9% but low specificity and predictive value. Therefore, it was felt that platelet volume could not be used as a screening test in this low risk population.

It can be noted from Table 8.5 that the haematocrit similarly did not show any predictive value.

Cross Sectional Studies in PIH (Group E)

No change in these platelet parameters was seen in women with moderate PIH when compared to gestation matched controls (Table 8.7). A fall in platelet count ($p < 0.001$), but no change in MPV or PDW was seen in women with severe PIH under 34 weeks. Women presenting with severe PIH after 34 weeks had a smaller reduction in platelet count ($P < 0.05$) but a markedly increased MPV ($p < 0.001$) compared to controls. Women with PIH displayed similar postpartum changes in platelet count, MPV and PDW to those seen in healthy pregnant women with results returned to normal by six weeks postpartum.

In the serial studies, of the 34 patients with essential hypertension, 14 patients had worsening hypertension (Table 8.8) In the 8 patients, who had worsening hypertension but did not become severe, there was little change in the mean platelet volume but in the 6 patients who developed severe superimposed preeclampsia the MPV was significantly increased at least one week before it became clinically apparent (Table 8.8). The platelet count did not significantly fall when compared with the patients who remained stable. Similar findings were found in the mild PIH

group (Table 8.9). In the patients where there was a significant increase in MPV, suggesting an increased platelet turnover and platelet deposition within the placenta, there was an increased incidence of intrauterine growth retardation, with 7 of the 16 babies being smaller than the 10 th centile for birthweight. This is further evidence that it is in these progressive patients with platelet consumption that most of the pathology in PIH, particularly for the fetus, will be found.

8.5 Discussion

Giles (1981) found no change in platelet count or MPV in normal pregnancy. However, he did not analyse his patients according to trimester. The findings in these studies confirm the rise in MPV in late third trimester described by Fay *et al.* (1983) and Sill *et al.* (1985). These two groups also reported a progressive rise in PDW throughout normal pregnancy and Fay et al. (1983) found a reduced platelet count in the last 8 weeks of normal gestation.This study confirms a rise in the PDW only in the third trimester, but no change in platelet count was seen. The time-dependent changes in platelet volume and shape induced by EDTA anticoagulant (Rowan and Fraser, 1991) may explain differences in MPV and PDW between studies. The importance of analysing samples at a consistent time after venesection is clear. Even then, it is not established that normal and abnormal platelets respond to anticoagulants in the same way. The analysis of samples up to 18 hours after venesection as performed by Fay et al. (1983) may also affect platelet numbers.

As the majority of patients with PIH present in the third trimester, when normal pregnancy appears to induce changes in MPV and PDW it is important to compare these patients with gestation-matched controls. When this is done, no change is seen in platelet parameters in moderate PIH.

This study has demonstrated different patterns of platelet changes in patients presenting with severe PIH (preeclampsia) before and after 34 weeks. This has not previously been reported. However, Moore & Redman (1983) have suggested that PIH presenting before 34 weeks is more severe and may have a different natural history from late PIH. These findings are consistent with this suggestion. Patients with early severe PIH displayed a low platelet count, but normal MPV. The progression of the PIH in these patients may be so rapid that the patient presents before compensatory platelet changes can occur. An increase in MPV has been described in association with a 'compensated thrombocytolytic state' in a variety of clinical disorders (Garg, Lackner and Karpatkin, 1972) Patients presenting later with severe PIH may have a less rapid disease-process and display compensation with a less severe fall in platelet numbers but a rise in MPV suggesting an increase in platelet turnover.

Giles & Inglis (1981)described a rise in platelet numbers and a fall in MPV after delivery in patients with severe PIH. This study also demonstrated these changes in

PIH patients postpartum, but also revealed a similar rise in platelet count and fall in MPV and PDW after delivery in normal pregnancy. The marked fall in MPV occurs whether the MPV was previously in the normal range or elevated. An ergometrine effect on MPV can be excluded as many of the patients who displayed the postpartum reduction in MPV had not received ergometrine at delivery. Iron deficiency, in which increased small platelets have been described (Harker, 1968) was also excluded in these women. All values had returned to normal by 6 weeks. The rise in platelet count may be a response to blood loss during delivery but it seems strange that, if these are new platelets, the MPV became smaller.

The increased MPV in late third trimester of normal pregnancy followed by a fall to subnormal levels postpartum might suggest that compensated mild platelet consumption occurs in the last weeks of normal pregnancy. However, diminished platelet lifespan has not been detected in studies of normal pregnancy using an acetylsalicylic acid labelling technique (Wallenburg and Van Kessel, 1978). Events during thrombocytopoiesis appear to be the most important determinant of platelet size (Paulus, 1975) and a hormonal alteration in thrombocytopoiesis may explain the changes seen in pregnancy. Whichever explanation applies, large platelets appear to be more active than small platelets, irrespective of age. This study has demonstrated changes in platelet volume in the final weeks of normal pregnancy which represent a continuum with the changes seen in PIH. The platelet alterations reported in PIH may therefore not all be secondary but may be a factor in the pathogenesis or persistence of the condition. It obviously requires time for these changes to occur. The alterations probably occur in parallel to the disease development and the degree of progression may depend on the patient's ability to compensate for the disease changes. The patients that present in the late second or early third trimester of pregnancy, may be those with little ability to respond to the insult of the disease. This may be influenced by the ability to produce prostacyclin (see next chapter).

It is not surprising, therefore, that the prospective study did not give evidence of a significantly increased platelet consumption remote from the onset of the clinical disease. However, the fact that the MPV tended to be higher in the patients who progressed does suggest that there may be an early increase in platelet consumption in this group. It is, however, of no value as a screening test. Similarly, there was no evidence of an increased haematocrit being associated with the patients who developed serious hypertension as has previously been suggested. The serial study did confirm that there was increasing platelet consumption in the patients who developed moderate and severe PIH and the changes relating to this increased platelet consumption did antedate the appearance of clinical signs by at least one

week. Since there are other methods of investigation, such as uric acid (Redman, Beilin and Wilkinson, 1976), which can be used to help to monitor patients at risk of developing progressive PIH it is difficult to know whether mean platelet volume is necessarily any better than monitoring serial platelet counts and uric acid levels. It does, however, support the argument for the use of low dose aspirin in patients thought to be at risk as, if this reduces the degree of platelet consumption that occurs, it may slow or stop the progression of the disease to its more severe form, and reduce the chance of placental insufficiency.

8.6 Conclusions

The main conclusions from this chapter are:

1) Platelet size **increases in normal pregnancy** towards term.

2) There are larger increases in preeclampsia, but only in the **later onset group.**

3) The patients response to the disease may influence the **gestation of onset.**

4) Early onset disease may be a sign of **poor patient response**.

5) Platelet activity is a part of the disease process but **not the cause**.

6) Antiplatelet therapy may help to **attenuate** the disease process.

Chapter 9

Studies on Prostacyclin and thromboxane

9.1 Introduction

As discussed in Chapter 3, prostaglandins have long been known to have physiological roles in pregnancy and parturition. Many of the changes seen in PIH and IUGR, such as platelet consumption, vasoconstriction and low renin secretion may result from PGI_2 deficiency, as PGI_2 is a potent vasodilator, platelet inhibitor and renin secretion stimulant (Miyamori *et al.*, 1979) TxA_2 is produced from activated platelets and is a PGI_2 antagonist, having platelet aggregatory and vasoconstrictor properties (Hamberg, Svensson and Samuelsson, 1975). Prostacyclin's major metabolite is 6-keto-PGF1α. Thromboxane A_2 is converted to its stable hydration product thromboxane B_2 (TxB_2). Measurement of PGI metabolites has been, and remains a subject of great controversy. Initial work on 6-keto-PGF1α by radioimmuno- assay (RIA) suggested that levels in normal subjects were of the order of 70-100 pg/ml (Mitchell, 1978), and this was supported by gas chromatography-mass spectrometry (GCMS) which suggested similar levels (Hensby *et al.*, 1979). However, Blair *et al* (1982) using negative ion GCMS, showed that the absolute values for 6-keto-PGF1α were <5 pg/ml, and they concluded that PGI_2 could not be a circulating hormone in man as previously thought. This does not preclude a role for PGI_2 functioning as a local hormone in the regulation of platelet-vessel wall interaction. Changes in levels of its stable metabolites must reflect changes in production. It is still valuable to measure these metabolites to elucidate the role of prostacyclin in disease. RIA has also been discredited by varying 'normal' values due to differences in methodology and antibody sensitivity (Viinikka and Ylikorkala, 1982). While RIA cannot give absolute values for PGI_2 metabolites, the assay can still produce accurate comparative values.

Much improved RIA methods have been developed recently with sensitivities and normal levels much closer to that obtained by GCMS. RIA, therefore, can still yield much valuable and accurate data provided proper controls are included and validation performed (Salmon, 1983). It has many advantages over GCMS as it is relatively sensitive, specific, and can cope with large numbers of samples. For these reasons RIA is probably the method of choice for routine measurements (Belch *et al.*, 1983; Salmon, 1983). There is little information on the normal levels of PGI_2 and TxA_2 in pregnancy and since they may be implicated in disease processes, it is necessary to know the normal ranges. Lewis et al. (1980) published levels of 6-keto-PGF1α and showed an elevation in late normal pregnancy and the puerperium. Bolton et al. (1981) recorded serial measurements throughout 12 normal pregnancies, and found a peak at 18-22 weeks gestation with a subsequent reduction towards term. Both of these studies were carried out before the work by Blair et al. (1982) and suggested normal ranges of 80-200 pg/ml for 6-keto-PGF1α. These studies

are still quoted as normal ranges despite subsequent advances in knowledge and assay techniques. In view of these advances and the conflicting reports of Lewis et al. (1980) and Bolton et al. (1981), the aim of the studies reported here was to determine the comparative values of PGI_2 and TxA_2 metabolites throughout normal and abnormal pregnancy and the puerperium, using a RIA which has been shown to be sensitive, specific and reproducible for PGI_2 metabolites (McLaren *et al.*, 1985).

9.2 Patients and methods

Three separate studies were set up.

Normal cross-sectional Study

The study included 155 women; 44 normal nonpregnant, 29 women in the first trimester of pregnancy, 31 in the second trimester, 29 in the third trimester, and 21 women on the third day following delivery. All pregnancies were uncomplicated and no subject had taken any aspirin or similar preparations for at least 2 weeks before blood sampling.

Hypertensive Study.

Twenty-six patients with mild/moderate PIH, 15 patients with severe PIH (preeclampsia) and 40 normal pregnant women in the third trimester, were studied, the latter group acting as controls (Table 9.1). Mild/moderate PIH was defined as a persistent diastolic blood pressure greater than or equal to 90 mmHg after 3 days hospital bed rest in women who had been normotensive in the first trimester. Severe PIH (preeclampsia) was defined as a persistent diastolic blood pressure of greater than 110 mmHg in women who had been normotensive in the first trimester. Proteinuria was not used in the disease classification but was present in most cases. (Table 9.1)

Serial study

Fourteen randomly selected patients were studied, all were primigravida and had no history of any hypertensive or medical disorder. No subject took any aspirin or similar preparation for a minimum of two weeks prior to each venepuncture. Blood sampling was performed in the late first trimester (9-12 weeks gestation), the second trimester (17-24 weeks gestation) and in the 3rd trimester (32-36 weeks gestation). In the patients who became hypertensive further samples were obtained where possible between 36 weeks and term.

Sample Handling and Assays

Venous blood was taken without stasis into an anticoagulant mixture consisting of 3.8% w/v trisodium citrate containing $3x10^{-5}$ M indomethacin and 10^{-4} M adenosine (9 volumes of blood to I volume anticoagulant), and then centrifuged at $4^{o}C$ for 20 min. at 3000 r/min. Plasma prostacyclin metabolites (PGI_2M) were measured on

unextracted plasma by radioimmunoassay as described previously (Belch *et al.*, 1983; McLaren *et al.*, 1985). Lower limit of sensitivity of the assay is 5 pg/ml, recovery of added 6-keto-PGF1α was 95% (SD 9), intraassay variation is 4% and interassay variation 9%. TxB_2 was measured in unextracted plasma, by a RIA with a lower limit of sensitivity of 20 pg/ml, intraassay variation was 4%, and interassay variation 10%. It is a debatable subject in the field of RIA, whether plasma samples should be extracted or not, since many extraction procedures can add further impurities (Greaves and Preston, 1982), which can produce detectable levels of PGI_2M in distilled water blanks subjected to the same procedure. The assay we used has been shown to be sensitive, reproducible and specific for measurement of PGI2M directly in unextracted plasma, avoiding the technical difficulties associated with extraction procedures (McLaren *et al.*, 1985).

9.3 Results

Normal cross-sectional Study

Results for PGI_2M and TxB2 are shown in Table 9.2. There was a significant difference in PGI_2M levels in the first trimester ($p<0.01$) when compared with those in the non-pregnant group. While there were no significant differences between non-pregnant values and those in the second or third trimesters, a trend towards lower concentrations of PGI_2M on the third postnatal day was noted, but this also did not reach significance. Levels of PGI_2M were significantly lower in the second and third trimester and the puerperium than in the first trimester group ($p<0.05$). There was a progressive reduction in plasma TxB_2 concentrations from the second trimester, through the third trimester and into the puerperium.

Hypertensive study

The description of the patient groups in the cross-sectional study of PGI_2M in mild/moderate and severe PIH (preeclampsia) compared to normal third trimester pregnancy is seen in Table 9.1. The PGI_2M results are shown in Fig. 9.1 and the TxB_2 in Fig. 9.2. As can be seen, 11 of the 26 patients with mild/moderate PIH and 13 of the 15 patients with severe PIH had unrecordable levels (<5 pg/ml) of PGI_2M. No patient in the normal third trimester pregnancy group had unrecordable levels of PGI_2M. The levels of PGI_2M in both the mild/moderate and severe PIH groups were significantly different from those in the normal group. The majority of the patients in the severe group had unrecordable levels. The level of PGI_2M in patients with PIH was not related to parity, with both primigravida and parous women having unrecordable levels of PGI_2M. There appeared to be a trend towards a negative correlation of PGI_2M with proteinuria and a positive correlation with intrauterine growth retardation but this did not reach significance.

The TxB_2 results show that thromboxane appears to be increased only in the

mild/moderate group and not the severe group. (Fig. 9.2)

Serial Study

Of the 14 patients studied, 8 remained normotensive while 6 developed mild to moderate PIH in the 3rd trimester, defined as a persistent diastolic blood pressure of 90 mm of mercury. 5 were treated conservatively, while one required treatment with an antihypertensive agent (labetalol). None developed significant platelet consumption or proteinuria. All patients had vaginal deliveries either spontaneous or induced at term, and all infants were healthy with birth weights above the 10 th centile for their gestational age. The proportion of patients who became hypertensive was unexpected and extraordinarily high. There was no apparent reason for this as all were apparently normal patients at a routine antenatal clinic. The high incidence in the study group appears to be totally coincidental.

Results are shown in figures 9.3 and 9.4 with a fuller statistical analysis in tables 9.3 and 9.4.

In the normal patients PGI_2M was significantly higher in the first than in the second and third trimesters, while TxB_2 levels fell significantly in the second and third trimesters as compared with the first trimester. There was no significant difference for either PGI_2M or TxB_2 between the second and third trimesters of the normal group, although there was a trend towards lower levels of TxB2 in the third trimester. These results agreed with the previous cross-sectional study.

In the first and second trimesters, the PIH group was not significantly different from the normal group for either PGI_2M or TXB_2. All hypertensive patients developed unrecordable (<5pg/ml) levels of PGI_2M in the third trimester when they were hypertensive. In 3 of the 6 PIH patients hypertension had developed prior to the sample showing unrecordable levels, therefore it could not be determined whether undetectable PGI_2M levels preceded the development of hypertension or vice-verse. In the other 3 patients, however, unrecordable levels were measured prior to the development of the hypertension.

Owing to the small numbers and differing times of development of PIH it was not possible to compare statistically the third trimester measurements in the PIH patients with the normal group. The late (36-40 weeks gestation) third trimester measurement in the PIH group was significantly different from the first and second trimester measurements within the group. There was a significant reduction in TXB_2 in the second and early (32-36 weeks gestation) third trimester compared to the first trimester in the PIH group and a significant increase in TXB_2 was noted in the late third as compared to the early third trimester. There was no significant difference between normal and PIH groups for TXB_2, and no correlation existed between PGI_2M and TxB_2 in either group.

9.4 Discussion

Despite using larger numbers the cross-sectional study did not confirm the work of Lewis et al. (1980) who showed a higher concentration of 6-keto-PGF1α in late pregnancy and the puerperium. It also could not confirm the work of Bolton et al. (1981) as the peak levels of PGI_2M occurred in the first trimester, and not in mid-pregnancy as they reported, although they did not record levels before 14 weeks gestation. We found a significant difference in the first trimester compared with values in the nonpregnant and second and third trimesters. This early increase may be involved in the physiological vasodilation and insensitivity to angiotensin II (Gant *et al.*, 1973) which are characteristic of early pregnancy. It has recently been shown that trophoblast from early pregnancies has a high capacity to synthesise PGI_2, and it has been suggested that colonisation of maternal blood vessels by trophoblast is facilitated by PGI_2. which may prevent platelet aggregates from halting this process (Lewis, 1982) This theory might explain the findings of elevated PGI_2M levels in early pregnancy. Theoretically one might expect high levels of PGI_2 in late pregnancy, due to the potential for increased production from the uterus and fetoplacental circulation unit. This study did not show any increased levels at this stage. This may be explained by the findings of Remuzzi et al. (1981) who found a reduced level of prostacyclin stimulating factor in late normal pregnancy, possibly a homeostatic mechanism. Since the capacity to produce PGI_2 is increased at this stage, less prostacyclin stimulating is required. In the postnatal group a trend towards reduced levels was found which contradicts the work of Lewis et al. (1980). The sampling was performed only on the third postnatal day, while Lewis et al. (1980) sampled between the first and seventh postnatal days. If many of the samples were obtained soon after delivery they may have had a high 6-keto-PGF1α level due to vascular injury or the recognised rise of PGI_2 during labour (Ylikorkala, Makarainen and Viinikka, 1981). Since the fetoplacental unit, which has enormous capacity to synthesise PGI_2, is removed at birth, a reduction in 6-keto-PGF1α levels postnatally might be expected. There is also a fall in PGI_2 levels after suckling (Ylikorkala and Viinikka, 1981). There was a progressive fall in plasma TxB_2 concentrations throughout pregnancy and into the puerperium. This may reflect increased platelet stability, or the diversion of TxB_2 precursors into the formation of other prostaglandins, such as PGD_2 or PGE_1. Other possible explanations of this may be related to a change in activity of thromboxane synthetase or decreased substrate availability, but further studies are required to elucidate this.

The results in the patients with PIH confirm that low levels of PGI_2M occur in PIH, with over 50% of patients in this study having unrecordable (<5 pg/ml) levels of this metabolite, a feature not seen in the normal group. This did not appear to be

absolutely related to disease severity as 11 of 26 patients with mild/moderate disease and 13 of the 15 patients with severe disease had unrecordable levels. However, many patients in the mild/moderate group and 2 patients in the severe group had PGI_2M levels within the normal range, suggesting that very low levels of PGI_2M are not always found in PIH.

These findings are consistent with other studies. Yamaguchi and Mori (1985) studied 15 women with PIH and found them to have relatively lower levels of plasma 6-keto-PGF1α than normal pregnant women. However, the levels they reported were very high and bring the validity of their assay into question. Moodley et al (1984) also reported lower levels of plasma 6-keto-PGF1α in women with eclampsia or impending eclampsia compared to normal pregnancy, but again they reported very high levels of this substance although they were taken from central lines. Not all reports on plasma PGI_2 metabolites in PIH have been consistent. Ylikorkala et al. (1981) found no change in 22 patients with PIH compared with normal pregnancy. Strickland et al. (1984) reported higher levels of 6-keto-PGF1α in PIH. The findings of the present study are in keeping with the work of Goodman et al., (Goodman *et al.*, 1982) who studied 6 patients with PIH and found them to have lower levels of urinary PGI_2 metabolites. The reports of reduced amniotic fluid PGI_2 in PIH and reduced PGI_2 production from both maternal and fetal vascular tissue are also in keeping with the findings of the low PGI_2M in PIH seen in the present study. Low levels of PGI_2 may well play a role in the pathophysiology of PIH, as a deficiency of this vasodilator and antiplatelet prostaglandin might allow the vasoconstriction and platelet consumption, which are characteristic of PIH, to go unchallenged. PGI_2 may also be important in balancing the pressor effects of angiotensin II in normal pregnancy (Broughton Pipkin, Morrison and O'Brien, 1984), although similar effects have been found for PGE_2 (Broughton Pipkin *et al.*, 1984) and PGE_1 (Broughton Pipkin, Morrison and O'Brien, 1987). Therefore, prostacyclin may be an important vasodilator during pregnancy. The reduced levels of PGI_2 in PIH seen in the present study may explain the AII sensitivity seen in PIH. This is another mechanism by which PGI_2 deficiency could contribute to the disease process in PIH. A cause and effect relationship between low PGI_2 and PIH cannot be concluded from this present study and other prostaglandins may also be involved. PGI_2 deficiency is unlikely to be the primary cause of the disease, but may occupy a pivotal role in the pathophysiology of PIH, by increasing vascular sensitivity and allowing vasoconstriction and platelet consumption to occur unopposed.

The results from this small prospective longitudinal study show increased concentrations of plasma PGI_2M in the first trimester, and falling levels of plasma TxB_2 in the second and third trimesters of normal pregnancy. This confirms the

results found in the cross sectional study. Prostacyclin may play an important role in implantation and establishment of normal pregnancy.

All hypertensive patients developed unrecordable levels of PGI_2M and this is consistent with the cross-sectional study. As three patients had unrecordable levels of PGI_2M prior to development of PIH, this suggests that falling levels of PGI_2M may antedate the development of hypertension, and may possibly act as a marker, heralding the development of the disease. Thromboxane A2 did not seem to be related to PIH. A significant increase in the late third trimester of the hypertensive group was noted. It is not possible to comment as to whether this was related to the disease, due to subclinical platelet aggregation, or was a normal finding as we did not have a late third trimester sample in our normal control group. It would appear that the change of prostacyclin/thromboxane balance is more related to a fall in prostacyclin than a rise in thromboxane.

The fact that prostacyclin levels are higher in the second trimester in the patients who developed PIH compared to those who did not, suggests that there may be an increased demand on PGI_2 production at that time. This could be due to increased vasoconstrictor activity. It is when this ability to respond is lost that PIH develops. The earlier this ability is lost or the greater the demand, the earlier the disease develops. This theory would fit the data in these studies. The severe early disease group almost always had unrecordable levels whereas the later more moderate group had mixed results. These results also fit those found in the platelet size studies (Chapter 8) where the early disease group had no changes in platelet size and the later onset disease had larger platelets. These are the patients who can compensate for the disease stimulus. However, there will be an increase in their platelet consumption leading to changes in platelet size.

Therefore, prostacyclin deficiency is unlikely to be the cause of preeclampsia, but may be the factor that effects the way the disease presents and how severe the patient becomes. This would imply that there are two factors involved, a stimulus or trigger, and the response or susceptibility. The factors affecting prostacyclin production would contribute to the susceptibility to the disease. The stimulus could possibly be mediated through the renin/angiotensin system as postulated by Symonds et al (1978) and discussed in Chapter 3.

9.5 Conclusions

The main conclusions from this chapter are:

1) In patients with severe preeclampsia, **prostacyclin production is deficient.**
2) This low level of prostacyclin can be seen in **some of those with milder disease.**

3) The low level of prostacyclin may be due to an **absence** or a **loss** of production ability.
4) The **response** a patient has to the disease process may depend on their **ability to produce** prostacyclin.
5) Some factor appears to **reduce the ability** to produce prostacyclin.
6) Thromboxane elevation is a **late manifestation** of the disease.
7) The alteration in the **prostacyclin/thromboxane balance** is mostly due to **loss of prostacyclin.**
8) These findings appear to **agree with the platelet size studies.**

Chapter 10

Studies of Management of Pregnancy Hypertension

10.1 Introduction

The results of the daycare studies suggest that the risk of hypertension in pregnancy is greatly overestimated. The majority of patients who are diagnosed as having mild to moderate hypertension remain relatively stable and at low risk for the rest of their pregnancy. By close monitoring of this group, it appears to be possible to determine those who will remain low risk from those who will progress to the moderate or severe stage. Therefore, the development of severe preeclampsia with proteinuria may be predicted, or perhaps prevented. If a significant number of patients progress from milder stages to more severe forms, it may be possible to develop systems of early recognition and intervention in this condition. However, there will remain patients in whom severe preeclampsia appears without a previously recognised mild stage.

Therefore, it would seem logical that, if patients are thought to be at risk of development of severe preeclampsia, they should be monitored closely for signs of progression of disease and signs of placental insufficiency which may interfere with fetal growth and wellbeing. If all parameters remain stable and fetal growth is satisfactory, the patients may be allowed to continue their pregnancy and so reduce prematurity, even though they have obvious stigmata of developing preeclampsia.

At the initiation of these studies, the main risk to the mother was of the hypertension itself since the main cause of maternal death was cerebrovascular accident (Turnbull, 1987). The risks to the baby, however, consists of prematurity due to iatrogenic delivery because of the maternal condition, placental abruption or placental insufficiency and intrauterine growth retardation (Common Services Agency, 1986).

Most patients could be managed by close monitoring, with delivery if there are signs of fetal compromise, or concern about maternal wellbeing. If placental function is adequate, antihypertensive drugs may help to reduce the maternal risk and further prolong the pregnancy.

To try and establish this system of surveillance, a stepwise approach to the management of hypertension in pregnancy has been developed. The aim was to monitor closely those at risk, develop guidelines for management and delivery and investigate the role of antihypertensive drugs.

10.2 Methods

All patients who were seen at the antenatal clinic and found to have an elevation of blood pressure above 140/90 mmHg were referred initially to a day assessment unit. At this attendance, an assessment was made of the risk to both mother and baby as previously described in Chapter 7. If the risk was thought to be low, the patient was referred back to the care of her obstetrician at the antenatal clinic. If the risks were

assessed as moderate the patient continued to be monitored at the day assessment unit. If the risk was assessed as high, she was admitted to hospital for closer monitoring and stabilisation of her condition.

If blood pressure was persistently elevated, various studies into the effect of antihypertensive drugs were carried out. Following these studies, general protocols of management were developed.

10.3 Acute studies

The use of antihypertensive drugs in pregnancy has generally been within the 'fire-station' approach, that is only when the blood pressure is severe (Garden, Davey and Dommisse, 1982; Thien *et al.*, 1980). The traditional drugs used have been hydrallazine (Reti *et al.*, 1987; Joyce and Kenyon, 1972) and diazoxide (MacLean *et al.*, 1981; Rabau Friedman *et al.*, 1980). A study was set up to look at oral alternatives to these parental drugs.

Methods

Thirty patients, in the third trimester of pregnancy, who had diastolic blood pressures above 105 mmHg on 2 measurements after 30 minutes of bed-rest were randomised to treatment either with 200 mg oral labetalol or with 10 mg intramuscular hydrallazine. A separate study of 10 mg of oral nicardipine, the calcium channel blocker, was carried out in 20 patients with the entry same criteria. (Table 10.1)

Pulse and blood pressure were monitored every 15 minutes for 2 hours after the drug was given. No other drugs were used during the period of observation. Measurements on individual patients were carried out by one observer. Phase four Korotkov sounds were used for the diastolic measurements in all cases, and the blood pressure taken in the left arm with the patient sitting at 45 degrees throughout the 2 hours.

Results

The studies into the use of labetalol, hydrallazine and nicardipine demonstrate that all three drugs produce a smooth predictable fall in diastolic blood pressure (Fig. 10.1). The blood pressure effect is seen within 10 minutes with the full effect seen at 30 minutes. The effect is still apparent at 2 hours. Both nicardipine and hydrallazine produced an initial rise in the systolic blood pressure compared with their own baseline, but there was no statistical difference between the three drugs and the effects were similar by 90 minutes. The effect on the pulse rate was also different (Fig.10.2). Labetalol produced a small initial rise in pulse rate but overall there was no change. There was a significant rise in the pulse rates seen with nicardipine and hydrallazine at 30-60 minutes but there was no difference after 90 minutes. (Fig. 10.2).

More patients given labetalol or nicardipine subjectively felt better following

medication compared with those given hydrallazine. Also, fewer complained of side effects (Table 10.2).

Six patients given hydrallazine complained of headache, nausea or tremor. The rise in pulse rate, combined with the increased pulse pressure, could explain the headaches seen with hydrallazine. However, only 2/20 patients experienced headache or other side effects after nicardipine despite similar cardiovascular actions.

10.4 Early treatment of Pregnancy Induced Hypertension.

After admission to hospital, the traditional treatment consists of bed rest (Turner, 1981b). The benefit of this has been questioned (Hamlin, 1952; Matthews, 1977a). Antihypertensive drugs are normally only used in severe hypertension (Chamberlain *et al.*, 1978a). In order to study whether earlier more active blood pressure reduction would have more benefit than bed rest alone, an open randomised study of traditional bed rest against antihypertensive treatment using oral labetalol (± hydrallazine) was set up. An open study was chosen instead of a placebo controlled study because, at the time, there was little information on the dosage required to control blood pressure. It was expected that a certain number of the patients would need maximum doses of labetalol plus hydrallazine.

Methods

A total of 126 patients were recruited to the study, 74 primigravida and 52 parous patients. The criteria for entry was an average daily blood pressure of over 95 mmHg after four days of hospital bed rest in the third trimester. All patients had had a normal first trimester blood pressure. Primigravida and parous women were randomised separately. Both groups were prescribed "Bed Rest". This consisted of "UTTAM" - Up To Toilet And Meals.

Treatment with labetalol was started at 100 mg. twice a day and increased in stages to 1,600 mg per day or until blood pressure control was achieved.

If control was not achieved or was lost at the maximum dosage, hydrallazine was added at a starting dose of 25 mg three times a day and increased until control was achieved to a maximum dose of 200 mg. a day.

Control was defined as either a fall in the average diastolic blood pressure to below 90 mmHg or a drop of 10 mmHg, from the starting diastolic blood pressure.

Loss of control was defined as a rise in the diastolic blood pressure to over 5 mmHg above the pretreatment diastolic blood pressure.

All patients entering the trial were closely monitored before and after starting treatment. The mothers were fully monitored and the effects, if any, on the cardiovascular, renal and coagulation systems were assessed. Placental function and the influences on the fetus and the newborn were also monitored as previously

described in Chapter 7..

Results

The patient groups were evenly matched (Table 10.3). Not only was the average diastolic above 90 mmHg, but the average blood pressures rise was above the 15 mmHg diastolic criteria of the American College used in the definition of preeclampsia (Hughes 1972). The average levels of uric acid and platelet count were not outwith the normal range for the gestation.

Oral labetalol at a dosage of 100 mg bd failed to control the blood pressure in any of the patients and although 100 mg tid efficiently lowered the blood pressure in some patients, the majority required 200 mg to achieve adequate control (fig 10.3). Overall, the treated group achieved blood pressure reduction within the first seventy-two hours and sooner than that once the starting dose was increased to 200 mg tid (fig.10.4). Fifty nine of the patients (92%) treated with labetalol had a blood pressure that fell into the normal range or remained at or around 90 - 95 mmHg (Table 10.4). Five of the patients showed signs of progressive disease, with a rise of diastolic blood pressure of more than 5 mmHg, requiring increasing doses of labetalol without complete satisfactory control. Of these, 2 patients developed severe preeclampsia with blood pressures over 110 mmHg and 4 of the patients developed proteinuria of greater than 0.3 gm/24 hours. In the control group the blood pressure remained elevated in the majority of the patients although the blood pressure did fall back into the normal range after continuous hospital bed rest in 9 patients. A further 20 of the patients remained with blood pressures within the moderate range and did not progress to worsening disease. However, 33 of patients had a steadily increasing blood pressure, and 20 were given intervention therapy at a later date. Of 33 patients with worsening disease, 13 developed severe hypertension with blood pressure rising over 110 mmHg and 9 patients developed proteinuria (Table 10.4). A significant improvement ($p<0.005$) was seen in the creatinine clearance in the treated group compared with the control group in which there was a slight but insignificant fall. (Fig 10.5). There was no difference seen in the changes in the levels of uric acid which rose in around 50% of both groups. There was a significant reduction in platelet count in the control group which not seen in the treated group ($p<0.005$) (fig. 10.6).

The side effects seen were all in the treated group, but there were only 4 withdrawals, 1 for bronchospasm, 2 for tremor and one at patient request, no reason given. (Table 10.5)

Fetal monitoring, as assessed by fetal movement counts, cardiotocographs and ultrasound estimation of fetal growth, showed no difference between groups.

There was no difference seen between groups in any aspect of labour, delivery or fetal wellbeing (Table 10.6).

It is to be remembered that many of the patients in the control group who progressed to more severe disease were then started on labetalol therapy to control the blood pressure. This may have helped to prolong the pregnancies in the control group.

Discussion

This study suggests that labetalol can be safely used in pregnancy. It can lower blood pressure successfully and appears to attenuate some of the progressive changes that are normally seen in PIH. However, since others still progress, the underlying disease process is still continuing. The changes seen in the creatinine clearance were not reflected in changes seen in uric acid levels, suggesting that uric acid abnormalities are not completely associated with renal function disturbances. The maintenance of the platelet numbers might suggest reduction in platelet consumption. In parallel studies, it was shown that labetalol does appear to have an affect on platelet aggregation (Greer *et al.*, 1985b; Greer *et al.*, 1983; Greer *et al.*, 1987) and this has been confirmed by others (Anfossi *et al.*, 1988). This finding might suggest a beneficial effect of labetalol apart from lowering blood pressure (De Sweit, 1985).

However, since the outcome in both groups was the same, there is no evidence to support starting treatment in mild disease. It would appear to be possible to closely monitor these patients in the daycare unit and delay intervention until patients have persistent blood pressures above 100 mmHg before commencing therapy.

10.5 Severe Study

If antihypertensive therapy can reduce or slow some of the disease changes, can pregnancies complicated by severe preeclampsia be stabilised and maintained safely with the help of antihypertensive drugs? A randomised study of drug therapy against non-treatment or placebo was considered. However, as antihypertensive therapy is commonly given if the diastolic blood pressure rises above 110 mmHg (Chamberlain *et al.*, 1978a; Mabie *et al.*, 1987; Garden, Davey and Dommisse, 1982; Michael, 1979), it was felt that it was unethical to withhold antihypertensive therapy from the majority of these patients. Therefore, the study was specifically designed to discover whether lowering blood pressure alters the disease process, allowing prolongation of the pregnancy and improving the outcome of the mother and baby.

Methods

To investigate the benefit of antihypertensive therapy in severe disease, 186 primigravidae with persistent diastolic blood pressures of over 110 mmHg or diastolic blood pressures of over 100 mmHg with proteinuria of at least 0.5 gm in 24 hours were commenced on oral labetalol.

All patients were assessed for fetal wellbeing prior to commencement. If there was any sign of fetal compromise, delivery was expedited and the patients were not included in the study.

The starting dose was 200 mg tid increasing to 1600 mg a day. If blood pressure control was not achieved a vasodilator was added. Initially this was hydrallazine 25 mg tid increasing to 200 mg/day as previously described. Then nifedipine was used at a starting dose of 10 mg bd increasing to 40 mg/day. Subsequently, nifedipine slow release 10 mg bd has been used.

Results

The patient group is seen in table 10.7. The parameters confirm that the patients had severe preeclampsia by most criteria. After commencement of labetalol, adequate blood pressure control was achieved in the majority of patients. Thirty three had a fall of diastolic blood pressure down into the normal range (less than 90 mmHg), a further 81 of the patients had their blood pressure reduced into the moderate hypertensive range between 90 - 100 mmHg (Fig. 10.7). In some of these patients long term control was achieved and they were managed as outpatients (Fig. 10.8). Fifty eight patients achieved adequate blood pressure control initially, although they required increasing doses and the addition of vasodilator substances to help maintain the blood pressure. In these patients, control was only achieved for around 10 days of therapy. In 12 patients blood pressure control could not be achieved within 48 hours of commencement of therapy and these patients were then delivered. The average dose of labetalol was 1201±320 mg (Range 600-1600 mg). As the study progressed, it became obvious that it was better to add nifedipine to the regime when the labetalol dose was 1200 mg rather than increase the labetalol alone. (fig 10.9)

In the 43 patients that received nifedipine as a second line drug, further blood pressure control was achieved with further prolongation of the pregnancy for another seven days (fig 10.10). Smoother control was achieved especially when nifedipine slow release 10 mg bd was used.

In the overall study, the average length of treatment was 15.6 days leading to a delivery gestation of 33.5 weeks (Table 10.8). It was not possible to predict those who would respond well to therapy and it did not appear to correspond to the other parameters of disease severity such as proteinuria, uric acid or platelet count.

After commencement of therapy, there was no change in uric acid, plasma creatinine or creatinine clearance although there was a slight deterioration just prior to delivery (Table 10.9). The average proteinuria did not change although in some patients the proteinuria disappeared whereas in others it steadily worsened. Generally if the proteinuria was less than 1.5 gm/24 hours and the blood pressure was controlled, proteinuria would disappear. As was found in the mild/moderate study, the platelet count rose after treatment was started. Sometimes this was dramatic (Fig. 10.11)

Close monitoring of the fetus was carried out throughout the study. If there was

evidence of fetal compromise as demonstrated by cardiotocograph abnormality, no improvement was seen even when blood pressure was controlled. In these situations, delivery was expedited for the benefit of the fetus no matter what the maternal blood pressure was.

There was 1 intrauterine death in a patient who suffered an abruption at 30 weeks. The patient was normotensive at the time after 2 weeks of antihypertensive therapy. There were 3 other birth related deaths, 1 a neonatal death at 4 days following a birth at 28 weeks and 2 other babies that died around the age of 3 months because of problems with long term ventilation.

Discussion

This study demonstrates that is possible to lower the blood pressure even in severe preeclampsia. In some patients, the blood pressure returned to normal and control appeared to be easy. This may call into question whether these patients had significant disease. However, there was no correlation between the severity of the disease at entry and the ease of blood pressure control. With most of the patients, control or stabilisation was achieved. This allowed the option to continue the pregnancy with a reduced risk to the mother. Many of these patients could be returned home and followed at daycare. This obviously has benefits to the patient. Prolongation of the pregnancy allows a more controlled timing of delivery and increased maturity of the fetus. The effects of this regime will be discussed later in this chapter.

One of the fears of antihypertensive therapy has also been the potential harm it might bring to the fetus (Lieberman *et al.*, 1978; Vink, Moodley and Philpott, 1980; Witter, King and Blake, 1981; Dagbjartsson *et al.*, 1985; Dagbjartsson, Kjellmer and Rosen, 1987). There was no apparent affect seen in this study as measured by cardiotocograph and ultrasound. If antihypertensive drugs do have an effect on the fetus, it is likely that it would be on the cardiovascular system. With new direct methods of studying fetal/placental blood flow (Fitzgerald and Drumm, 1977; Campbell *et al.*, 1983; Hanretty and Rubin, 1989), it is possible to investigate the effect of therapy on the maternal and fetal cardiovascular system.

Special Investigations

Various specific investigations were carried out into the effect of antihypertensive therapy on the mother and fetus apart from the routine investigations reported in Chapter 6.

Doppler assessment of the Effect of Antihypertensive Treatment.

If antihypertensive therapy is used to lower the blood pressure and reduce the maternal risks, pregnancies can be prolonged allowing the fetus to reach greater maturity. The reduction of blood pressure does not treat the underlying disease and

continuing monitoring of the mother and fetus is necessary. The main concern about antihypertensive therapy is the potential effects on the fetus, either directly or by a reduction in uteroplacental blood flow.

As described in Chapter 3, various studies have demonstrated both the risks and the lack of problems from the used of antihypertensive drugs.

Doppler ultrasound examination is a non-invasive procedure that permits the assessment of both maternal and fetal cardiovascular system. Abnormalities of Doppler waveforms have been reported in pregnancies complicated by hypertension. The aim of this study was to monitor the effects of acute and chronic blood pressure reduction on the maternal and fetal circulations using Doppler ultrasound.

Acute Study

Eight primigravid patients with acute hypertension in the third trimester of pregnancy were recruited. All had a diastolic blood above 105 mmHg for 30 minutes on bed rest in the semirecumbent position. The patients remained in this position and were given 10 mg oral nicardipine, a calcium channel blocker. The blood pressure, pulse rate, cardiotocograph and Doppler waveform analysis of the uteroplacental, maternal brachial and fetal umbilical arteries were carried out before and during the 60 minutes following the administration of the drug.

Chronic Study

Fifteen primigravid patients with mild preeclampsia were recruited. All had an average daily diastolic blood pressure of greater than 100 mmHg and a gestation between 30 and 36 weeks. They were treated with the beta-blocker Pindolol, with a starting dose of 5 mg twice daily increasing to a maximum of 10 mg three times a day or until the average daily diastolic blood pressure was less than 100 mmHg. The same investigations as in the acute study were carried out before, the day following and on alternate days of pindolol therapy.

Control Group

There was no control group of patients for the acute study. For the chronic study, 15 primigravid patients with untreated mild preeclampsia were used as controls. All had an average daily diastolic blood pressure of between 90 mmHg and 99 mmHg and a gestation between 30 and 36 weeks. They were monitored using the identical methods as described above.

Doppler Waveform Analysis

Doppler ultrasound examination was performed using a continuous wave system (Doptek, Chichester, UK). A 150 Hz high pass filter was used to eliminate low frequency signals caused by vessel wall movement. During all Doppler studies, patients adopted a semirecumbent position with a 15 degree left lateral tilt to avoid caval compression. Umbilical artery and uteroplacental Doppler waveforms were

recorded. Doppler waveforms were obtained from the left maternal brachial artery located in the antecubital fossa. The systolic/diastolic ratio (SD) was calculated when five representative consecutive wave forms had been obtained from each vessel studied.

Doppler assessment of the Effect of Antihypertensive Treatment.

Acute Study

Administration of nicardipine was associated with a significant fall in the diastolic blood pressure by 30 minutes (Table 10.10). Diastolic blood pressures at 45 minutes and 60 minutes were also significantly lower compared with pretreatment values. As regards the Doppler readings, the only significant finding was a rise in the uteroplacental SD at 30 minutes. This change were not evident at 60 minutes.

Chronic Study

Following the administration of pindolol (Table 10.11), there was a significant fall in blood pressure seen within 24 hours but this control was not as good by 72 hrs. Control varied after this depending on whether the patients could tolerate higher doses of pindolol. The main reason for withdrawal of patients was marked beta-agonist side effects such as tremor. By 8 days, the number of patients remaining in the study make the results more difficult to interpret. The only significant change in Doppler measurements was a rise in the uteroplacental SD at 3 days. This change was no longer evident by 5 days.

When the control group were studied (Table 10.12), it can be seen that conservative management made little difference to the blood pressure, which rose steadily over the study period. With respect to Doppler indices, there was a significant rise in the uteroplacental SD at 5 days and the umbilical SD at 7 days.

Discussion

It would be surprising if therapy to lower blood pressure was not associated with maternal and fetal circulatory changes. The magnitude of such changes and their effect on fetal wellbeing must be influenced by the pharmacological properties of the drugs used, the rate of onset of antihypertensive action and the inherent ability of the mother and fetus to compensate for drug induced circulatory changes.

Most of the reported adverse fetal effects of antihypertensive therapy have been associated with acute lowering of maternal blood pressure. In the acute study, a rise in uteroplacental SD was seen 30 minutes after administration of nicardipine but this was short lived and was not reflected in changes seen in the umbilical blood flow parameters or fetal heart rate monitoring. It may be that the maternal and fetal circulations that were studied were able to rapidly compensate for the effect of acute blood pressure lowering. These findings do not exclude the possibility that some patients with hypertension in pregnancy (particularly those with a reduced

circulating blood volume) may not be able to compensate for the circulatory changes induced by acute antihypertensive therapy. Consequently, they may show a sustained change in uteroplacental and/or fetoplacental Doppler indices and fetal heart rate abnormalities. All patients we studied showed normal baseline uteroplacental and umbilical artery Doppler indices throughout the study period. It may be argued that such patients have a relatively stable cardiovascular system and lowering maternal blood pressure is unlikely to produce changes in fetoplacental or uteroplacental blood flow velocities. In addition, even if no Doppler changes are detected, this does not mean that there has been no change in maternal or fetal cardiovascular function. Further studies are indicated to assess the effect of antihypertensive therapy on patients with abnormal fetoplacental and uteroplacental waveform patterns, particularly when the umbilical artery shows absent end-diastolic frequencies.

In conclusion, data is accumulating that if required, the use of antihypertensive therapy in pregnancy has no detrimental effect on either fetal wellbeing or neonatal outcome if the fetus is in good condition before treatment. Although acute administration of nicardipine and chronic administration of pindolol was associated with a change in the uteroplacental SD ratio, there was no change in umbilical artery or maternal brachial artery SD ratios. The rise in uteroplacental SD ratio was clinically insignificant since it was transient and was not associated with evidence of either maternal or fetal compromise.

10.6 Development of Management Protocols.

After all these studies, an attempt was made to standardise the management approach and produce protocols that are simple to use. Inevitably, these protocols are under constant review. The final conclusions will be described although it is realised that these also may change in the future.

It is sometimes not possible to distinguish between the two forms of pregnancy hypertension. However, it is easy to separate the patients into those that present before 20 weeks and those that present for the first time at a later gestation. The later group are obviously not a "pure group" but the potential risks and therefore the management of these patients are similar. Antihypertensive therapy is only part of the overall management and should not be considered in isolation. Lowering blood pressure does just that, it does not cure the patient. The assessment and monitoring of the mother and baby is the most important part of any therapeutic regime. If there is any sign of maternal or fetal compromise, delivery should be expedited.

Patients presenting before 20 weeks or Chronic hypertension

If it was possible, any patient with chronic hypertension and who was on antihypertensive therapy was seen prior to pregnancy and the need of treatment

assessed. The patient may have mild disease and not require therapy and there are some drugs which are contraindicated. Any change of therapy should be balanced against the reason why the patient was given it in first place. If enalapril is the only drug that controls the blood pressure, then it may be better to continue this therapy even with the knowledge that it may cause problems. The need for therapy should be reassessed after the patient has become pregnant as blood pressure may fall in the first and second trimesters and need for therapy will be reduced.

If the patient's blood pressure is stable prior to pregnancy, she is continued on her medication and then reassessed in the first trimester. If the blood pressure has fallen below 140/90 mmHg, the therapy is stopped and restarted only if the blood pressure rises again to over 150/100 mmHg. (Table 10.13)

If the hypertension is diagnosed in the first trimester, the patient should be assessed for renal disease as this is often discovered for the first time during pregnancy. As long as the blood pressure is less than 150/100 mmHg, the patient is observed without therapy as it will normally drop by 18-20 weeks.

All patients with chronic hypertension in the GRMH are followed closely in the Outpatient Daycare Assessment Unit (Chapter 7). They are seen on a regular basis and monitored for both maternal and fetal wellbeing. (Table 10.13) If the blood pressure rises above 150/100 mmHg, antihypertensive therapy is started. Close monitoring as an outpatient is continued as long as stabilisation of the blood pressure is achieved. When treating chronic hypertension, the drug used probably does not matter very much. Although the use of antihypertensive drugs is unproven, it is our policy to treat patients if the blood pressure rises above 150/100 mmHg. The drug normally used is labetalol. This preparation has the advantage that it can be used in the acute situation as well as the chronic setting. It can be given by the intravenous route as well as orally. This means that medical staff only require to learn one regime for all patient groups. The starting dose is 200 mg eight hourly, increasing to 200 mg six hourly and then 300 mg six hourly. If control is not achieved or is lost at this dose, nifedipine, a calcium channel blocker, is added at dose of 10 mg retard twice a day increasing to 20 mg twice a day.

Patients presenting after 20 weeks.

Preeclampsia is a multisystem disease and the blood pressure is one aspect of it. All hypertensive patients are reviewed by the hypertensive team under the direction of the author. Only patients with a persistent blood pressure over 150/100 mmHg were considered for therapy. In the last 9 years, 3885 patients with hypertension in pregnancy have been assessed and only 649 of these have been started on regular doses of antihypertensive drugs. This constitutes only 16.7% of the hypertensive patients or 1.7% of the pregnancy population (Table 10.14. Approximately a further

300 (0.8%) have been given single doses of either labetalol, nicardipine or hydrallazine. Therefore, even if a 'liberal' approach to antihypertensive therapy is used the numbers treated are small. This is comparable with the rate of around 16% of patients given magnesium sulphate in some centres in the United States.

The regimen developed for the management of patients with preeclampsia in GRMH is the same as previously described for chronic hypertension. Over 60% of the cases treated were controlled on labetalol alone with a further 35% patients requiring a vasodilator, usually nifedipine (Fig. 10.9). As with all therapies, about 5% of cases were treatment failures and progressed to delivery because of poor blood pressure control. An integral part of the care of these patients, was the continuing close monitoring of the mother and fetus using a standard protocol (Table 10.13) The mother was monitored by platelet count, uric acid, urinalysis as well as regular blood pressure estimations. The average daily blood pressure (of four readings) was used as an assessment of blood pressure control and the need to change therapy. The occasional elevated reading was ignored. The fetus was monitored using the cardiotocograph and ultrasound estimation of fetal weight, biophysical profile and Doppler blood flow. Delivery was carried out when an adequate gestation was reached or when there was signs of either fetal distress or deterioration of the maternal condition. The average length of therapy continued to be 15 days, ranging from 24 hours to 8 weeks as first found in the initial studies.

The hypertensive crisis

Severe hypertension is a crisis for the mother, fetus, paediatrician and obstetrician. The aim of therapy was to stabilise the mother to reduce the risks to her and allow either prolongation of the pregnancy or delivery of the fetus in a controlled way. Any patient with a blood pressure above 160/110 mmHg, was given 200 mg of Labetalol. A fall of around 10/20 mmHg should be achieved within 60 mins. A further 200 mg was given as required. Alternatively, a slow intravenous injection of 50 mg labetalol was almost always successful in reducing blood pressure. This was followed by an infusion by a slow infusion pump delivering a solution containing 300 mg of labetalol in 60 ml, or 5 mg per ml if further therapy was required. This infusion was started at 12 ml/hr and increased or decreased depending on the blood pressure response. Control was normally achieved at a rate of between 24/48 ml/hr and we did not see any evidence of fetal distress in response to this regime. It is the author's experience that once a patient was started on an intravenous infusion to control the blood pressure, delivery was required as it was rare to transfer control to oral therapy.

The policy was to stabilise **all** patients with blood pressures above 160/110 mmHg prior to delivery or patient transfer as these are the times of great risk to the mother.

This is particularly true if a general anaesthetic with intubation is to be given. Therapy was continued after delivery as long as blood pressure control is required.

A single oral dose of nifedipine 10 mg or nicardipine 10 mg can also be used as the acute studies showed it to be effective. Occasionally, sublingual nifedipine was associated with sudden hypotensive reactions and oral therapy was safer.

Delivery

Delivery was carried out if there was any maternal or fetal reason. **This was done in the best way on the best day.** It was usually possible to plan this in collaboration with the paediatricians. If the patient is beyond 34 weeks, a vaginal delivery was aimed at. Before this gestation, or if there are signs of fetal distress, caesarean section would seem sensible to improve the fetal chances of survival. We found that the presenting gestation was the most important parameter affecting the fetal outcome. No baby born after 30 weeks gestation from a hypertensive mother has died in the last eight years. Most perinatal deaths are associated with low birth weight and early gestation as was discussed in Chapter 6.

Post delivery

After delivery, vigilance should be maintained. Many of the maternal deaths associated with this condition occur after delivery. The dosage of hypertensive drug would usually be reduced in a stepwise process until it can be stopped. If the drugs are suddenly stopped, rebound hypertension can occur with the concomitant risks to the mother. Most of the drugs used are excreted in the breast milk but appear to be safe to use in breast feeding mothers. Some patients became more hypertensive after delivery and were more difficult to control. In these situations enalapril was sometimes used. The starting dose was 2.5 mg twice a day, increasing in steps until control was achieved. If patients did not settle after delivery, the diagnosis was reconsidered and the patient referred for further investigation and management.

The effect of this therapy

Has this therapy and these protocols been beneficial? The effects of therapy on the patient population cannot be separated from the other changes in the management protocol, particularly the maternal/fetal monitoring. The summary of the results for the years 1980-89 are shown in table 10.14. The numbers of patients with persistent hypertension (diastolic blood pressure persistently above 90 mmHg) has remained constant over this time. Overall only 15.27% of hypertensive patients received antihypertensive therapy. However, in the last 5 years this has been about 20% of the patients. Prophylactic anticonvulsants were used in less than 100 patients. Despite this the rate of eclampsia in hypertensive patients was only 9/4317 or 1/438 during this period. This has reduced further to 1/577 since 1982, but this change was not significant.Therefore the change of management regimes has not

reduced the progression to eclampsia, but the risk appears to be small.

Perinatal mortality was only 7.2/1000 for all hypertensives over these ten years reducing to around 3/1000 in the last few years. If the years 1980-82 are compared to years 1983-89, there has been a statistically significant decrease from 14.07 to 4.25 per 1000 hypertensives ($p<0.001$). Since the incidence of hypertension has not changed, the rate of hypertensive deaths per 1000 of all deliveries has also fallen (Fig. 10.13). Comparisons with the Scottish figures show that GRMH rates were higher earlier in the decade but now have fallen to similar levels to the Scottish figures. This is in spite of the fact that apart from 1983, the GRMH figures for total PND rates have been consistently higher than the Scottish figures ($p<0.001$) (Fig. 10.14). If the percentage of PND associated with hypertension is considered (Fig. 10.15) it can be seen that the results from GRMH were higher in 1980-82 but since then have been consistently lower. This was statistically significant ($p<0.001$). It can be concluded that there has been an dramatic improvement in the figures that are not seen in Scotland as a whole.

If the gestation at delivery is studied, it can be seen that there has been a reduction in the incidence of delivery of babies before 30 weeks ($p<0.005$), and a smaller change in the incidence of delivery less than 35 weeks ($p<0.05$) (Fig. 10.16). Prolongation of the pregnancy from below 30 weeks would allow increased maturity for the fetus with improved survival. If the total perinatal mortality is split into stillbirth and early neonatal death (Fig. 10.17), it can be seen that there has been a reduction in stillbirth ($p<0.05$) and a more significant drop in neonatal deaths (($p<0.005$). (Statistics calculated by comparing years 1980-82 and 1983-89, Fishers exact test). Therefore the reduction appears to be related to stillbirth as well as neonatal death. This implies that, not only has prolongation of pregnancy reduced prematurity, but also improved monitoring may have led to judicious delivery. Perinatal death is now almost completely related to the sick premature baby (Chapter 6).

10.7 Discussion

Reluctance to administer antihypertensive drugs in pregnancy has arisen from reports of possible detrimental effects on the fetus and neonate as discussed in Chapter 3. If antihypertensive therapy is going to be of benefit, it is when it allows stabilisation of the mother and prolongation of pregnancy.

These studies suggest that antihypertensive drugs are effective in lowering the blood pressure in pregnancy, although the numbers requiring treatment are relatively small. Delivery remains the only cure for established preeclampsia and drug treatment should only be used to lower blood pressure to minimise the risks for the mother and help reduce the need to deliver the premature infant. The combined alpha/beta blocker labetalol appears to be well tolerated. It has the advantage that it

can be used in the acute as well as the chronic situation but studies suggest that other drugs could also be used.. Lowering the blood pressure may moderate the progression of the disease but it does not stop it.

Severe preeclampsia presenting in the mid-trimester is associated with high perinatal morbidity and mortality. Aggressive management with early delivery may result in neonatal death or long term disability from complications of the prematurity. Conversely, attempts to prolong the pregnancy may result in fetal death or asphyxial death in utero. It was seen in Chapter 6 that if the fetus is already compromised, there appears to be no benefit in prolonging the pregnancy and delivery should be expedited. Therefore, even when blood pressure is stabilised, close monitoring of both the mother and the baby should be continued.

If antihypertensive drugs are of benefit, it should be apparent that more babies are now being saved. Without a properly controlled study, either with a randomised group of patients receiving labetalol or not, or looking at good cohort studies of before and after the addition of labetalol to the pharmacological armoury, it is impossible to say whether the presence of labetalol has been detrimental or beneficial. It would appear that there has been a dramatic improvement in perinatal mortality which has not been matched in the rest of Scotland. There is now a lower percentage of babies being lost in GRMH associated with hypertension than in the rest of Scotland. There has also been reduction in delivery prior to 30 weeks. The reduction in perinatal death is as much due to a reduction in stillbirth rate as neonatal loss. This would imply that the increased monitoring and judicious delivery, as well as antihypertensive therapy, have contributed in lowering perinatal mortality.

Once delivery has been carried out, the mother may need continuing therapy for a number of weeks. If blood pressure does not settle following delivery, the diagnosis may need to be altered and the patient referred for further assessment.

10.8 Conclusions

The main conclusions from this chapter are:

1) A **stepwise** management protocol is easy to setup and practice.
2) Most patients are **low risk** and do not require hospitalisation, antihypertensive drugs or anticonvulsants.
3) The risk of eclampsia is **low**.
4) Blood pressure can be **controlled with ease** in the majority of patients.
5) If the fetus is well, the **pregnancy can be prolonged** for an average of 15 days.
6) If there is evidence of **fetal compromise**, therapy has **no benefit**.
7) **Premature delivery** and **perinatal mortality** can be **reduced** by using these regimes.

Chapter 11

Discussion and Conclusions

11.1 Discussion

Hypertension is a common abnormality occurring in about 15% of all pregnancies. Despite a general improvement in fetal and maternal outcome, it is still a major cause of maternal and fetal mortality and morbidity in this country and throughout the world.

A critical review of literature was carried out to assess the current state of knowledge concerning the presentation and management of pregnancy hypertension. Areas were then chosen where there was either a lack or a discrepancy of knowledge and where further investigation might be fruitful. The aim was to clarify some aspects of the aetiology and presentation of the condition and to see whether it was possible to develop management protocols that could improve the outcome for mother and baby. The main areas of study were selected to assess various aetiological factors; look for special markers of increased risk in patients presenting with the condition; study various methods of monitoring both the mother and baby for signs of progression of the disease; assess the role of intervention therapy using antihypertensive drugs; and investigate the effect of this therapy on the disease process and outcome of pregnancy.

The initial critical review of the available literature showed there were major problems in the definition of pregnancy hypertension. There was no universal agreement on the method of diagnosis of hypertension or what level of systolic or diastolic blood pressure merited special care or intervention. There was disagreement on whether the rise in blood pressure from a booking visit or the absolute level of blood pressure was more dangerous. The other problem of blood pressure measurement was the method of measuring the diastolic blood pressure. The American literature generally accepts Phase V Korotkov sound diastolic whereas the British literature tends to favour the IV Korotkov sound. This obviously is a problem and there may be a difference of 5 - 10 mmHg of mercury between the IV and V sound. There is also a dispute over which position the patient should be in while taking blood pressure. The importance of proteinuria was well documented although it was difficult to know what relationship proteinuria had to maternal and fetal outcome. Oedema did not appear to be an important factor and therefore should be ignored in the assessment of the condition. Parity was seen to be important in the diagnosis of pure disease as a primigravid with proteinuric hypertension is far more likely to be a true preeclamptic than a parous woman with hypertension. However, the fact that parous women can also have preeclampsia tends to be ignored in most literature.

Eclampsia has had a falling incidence throughout the world. This has had a limited effect on maternal mortality as its importance as a marker of severity of disease has

probably been overstated. The risk to both mother and baby is more related to the degree of preeclampsia than to the occurrence of an eclamptic seizure itself.

The whole area of preexisting hypertensive disease and the role of superimposed preeclampsia was extremely confused. As blood pressure rises in late pregnancy anyway it is very difficult to be sure whether a patient has true superimposed preeclampsia or just a worsening degree of preexisting hypertensive disease. All these complications make the nomenclature of hypertension in pregnancy exceptionally difficult.

It was concluded, that for the purpose of our investigations and in reference to other studies, that the term **'preeclampsia'** would be used solely for the **primigravida** with hypertension occurring for the first time during pregnancy and generally with proteinuria. All other forms of hypertension would be termed **'pregnancy-induced hypertension'**, unless a known preexisting hypertension such as essential hypertension or renal disease was present.

In studying the available literature on the aetiology of pregnancy hypertension I found that there were major degrees of overlap as various people were investigating various epiphenomena which were interrelated. They then would associate cause and effect with these changes, despite the fact that they are probably just markers of disease process. There are, however, various absolutes which merit further investigation.

1) There was a definite suggestion that preeclampsia was a hereditary disorder (Chesley and Cooper, 1986).
2) The epidemiology of the disease suggests that it has a strong immunological basis since it affects primigravid rather than parous women (MacGillivray, 1961) and factors such as blood transfusion appear to protect against disease development (Feeney, Tovey and Scott, 1977).
3) When the disease presents it appears to be associated with definite placental pathology which is not unique to preeclampsia but also is associated with intrauterine growth retardation (Sheppard and Bonnar, 1981).
4) In the presence of proteinuria there is a specific renal lesion which can be used as an absolute diagnostic marker of preeclampsia (McCartney, 1964).
5) There is strong evidence that there is increased vascular reactivity which appears to be present prior to the development of the disease itself (Gant *et al.*, 1973).
6) This vascular reactivity may be associated with prostaglandin and thromboxane imbalance (Downing, Shepherd and Lewis, 1980) which also would tend to increase platelet consumption, a sign which is well recognised in preeclampsia (Redman, Bonnar and Beilin, 1978).

On investigating the current information on the risks of pregnancy hypertension to the mother and fetus, it became obvious that most of the literature was historical and that the risk of death to the mother in the western world from hypertension in pregnancy is now not much greater than the risk of dying in pregnancy in general. However, it was also obvious that there had been little reduction in maternal death from hypertension in pregnancy over the 20 years from 1960 to 1980 (Turnbull, 1987).

As far as the baby is concerned, there has been a gradual improvement of outcome. This has mostly been due to improvement in neonatal care for the smaller baby. This produces a clinical dilemma. Although the potential outcome of hypertension in pregnancy can be catastrophic, for both mother and baby, the majority of patients now do well.

The literature on the management of hypertension in pregnancy was also mostly based on historical knowledge or came from centres seeing patient types quite different than those seen in Glasgow. Bed rest has remained the mainstay of hypertension management since the 1950's (Hamlin, 1952). The use of sedation and anticonvulsants was geared towards the time when eclampsia was seen as the main risk to the mother. Antihypertensive drugs have only more recently been introduced in routine management of this condition. Delivery is still seen as the only option by many in cases of severe hypertension with proteinuria and no attempt is made to stabilise the condition or prolong pregnancy.

Antihypertensive drugs initially were thought to be dangerous and associated with intrauterine death. More recently, a large number of studies with a wide variety of drugs have shown that antihypertensive drugs can be used without harm within pregnancy. Studies have been started on the use of aspirin as an antiplatelet agent in trying to prevent the development of preeclampsia. The initial results are encouraging but the outcome of the large multi-centre studies are still awaited.

It was obvious after this critical review of the literature that it was important;

1) to study the **absolute risk** of hypertension in pregnancy as seen in our own hospital.
2) to assess the problems of disease presentation to see whether it was possible to distinguish those who are at **increased risk** of maternal/fetal problems and **those who are not**.
3) to investigate the use of the **routine investigations** to see what information they can give us about **disease development**
4) to concentrate on certain areas of **aetiological significance**.

In order to investigate the changing risk to the mother and baby of hypertension in

pregnancy I reviewed 50 years of eclampsia at the Royal Maternity Hospital. I chose eclampsia as a disease marker because it was 'hard' and I could be relatively sure of the accuracy of the diagnosis whereas the diagnosis of hypertension is less reliable. I found that there had been a dramatic fall in the incidence of eclampsia from the mid 1930's to the early 1980's. Although this fall had been gradual and consistent, there was an increased reduction at around 1950. This coincided with the advent of the National Health Service and also the introduction of bromethol as a method of prophylaxis and treatment in patients with severe hypertension and/or eclampsia. There were 537 cases of eclampsia from 1933 to 1942, similar to numbers still seen in the third world (Lopez Llera, Linares and Horta, 1976). There were only 19 between 1973 and 1982, figures compatible with others seen in this country (Templeton and Campbell, 1979). Over the study period, 45% of the eclampsias occurred antenatally, 35% intrapartum and 20% postpartum. In recent years, there has been a relative increase in the proportion of postpartum eclampsia.

There were 74 maternal deaths in the first decade or about 14% of all eclamptics. There was only 1 maternal death in the last decade which is about 5% of all eclamptics. Therefore, not only has the incidence of eclampsia fallen dramatically, the maternal deaths from eclampsia have also fallen over that last 50 year period. This implies that the risk of eclampsia is now far lower in our practice than in other parts of the world. This has implications concerning the treatment of preeclampsia. The majority of maternal deaths were associated with antepartum eclampsia and this is usually related to the degree of preceding preeclampsia. Although the number of babies lost to mothers with eclampsia has fallen, one-third of the babies born to mothers with eclampsia in the last decade died. These figures are similar to the incidence in the first decade. This again is almost exclusively related to antepartum eclampsia, premature delivery or abruption. The conclusions from this study were that there has been a gradual improvement in the outcome of eclampsia over the last 50 years. The last maternal death in the Royal Maternity Hospital from hypertension in pregnancy was in 1964. This is almost in spite of any changes in therapy, although the use of bromethol and later other sedative drugs to try and stabilise the eclamptic appear to have had some beneficial effect. It would appear to be logical to move away from sedative therapy and concentrate on antihypertensive therapy in the first instance. If anticonvulsant therapy is to be used, a true anticonvulsant would appear to have some advantages.

I then went on to study the presentation of the disease in the present day. Initially, I looked at blood pressure variability. The serial study confirmed the normal fall in blood pressure in the second trimester, but the parous women did not have the same rise in the blood pressure in the third trimester. Therefore a diastolic blood pressure

of 90 mmHg at 32 weeks is more 'abnormal' in a parous woman than in a primigravida. A study at the antenatal clinic of 300 patients showed that over 60% of patients had a blood pressure variation of more than 5 mmHg in both systolic and diastolic blood pressure when 2 measurements were taken 10 minutes apart. The direction of variation depended on the level of blood pressure. There was a tendency to move towards the mean. I then went on to study repeated blood pressure measurements to see whether an average of several readings could give me a more accurate assessment. I again confirmed the blood pressure variations were quite marked on repeated blood pressure measurements. Once 4 blood pressure measurements had been taken and meaned, a fifth blood pressure reading did not change that mean by more than about 1 - 2 mmHg. Therefore, an average of 4 blood pressure readings appeared to give an accurate estimate of a patients' 'true' blood pressure. Variation in blood pressure has been documented before (Redman, Beilin and Bonnar, 1977a; Murnaghan, 1987), but methods of correcting for it have not. I also studied the use of automated blood pressure monitoring and showed similar variations to that found by nursing staff. The Dinamap automatic blood pressure recording tended to measure the diastolic blood pressure at about 8 mmHg lower than that found by the attendant nursing staff. This is probably due to the difference between the methods of diastolic blood pressure determination. The Dinamap records a diastolic blood pressure between the IV and V sound, whereas the nursing staff are taught to use the IV sound. Following this, I routinely used an average of 4 blood pressure readings taken over a space of a few hours for outpatients and over the space of a day for inpatients as a marker of a patient's blood pressure. I concluded that a single blood pressure reading should not be used as a method of diagnosis or of making management decisions. It would appear to be reasonable to use single blood pressure readings if epidemiological studies are being done.

Based on this philosophy, I conceived and developed an outpatient day assessment area to assess patients thought to be at risk of hypertension, with more accuracy. The day care unit started in a small way in 1981 and has gradually expanded to accept patients from all consultants in Glasgow Royal Maternity Hospital. At the day assessment unit, not only was blood pressure monitored, but also uric acid levels, platelet counts and proteinuria were estimated in the assessment of maternal risk. Fetal risk was assessed by cardiotocography and ultrasound. I found that, in the patients assessed at daycare, uric acid was rarely elevated and levels generally remained within the normal range. It was only after this monitoring had been carried out and abnormalities discovered and assessed that the patients were selected for the possibility of admission to hospital, and for investigations of early intervention therapy, in an attempt to control the disease process. Using the 3

parameters of blood pressure, uric acid and platelet count it was found that, if these were all within the normal range at day care, there was a 95% chance that these patients would remain normal throughout the rest of their pregnancy. This constituted approximately 50% of all patients who attended the day care unit. If any of these parameters were elevated, the patients were then seen back for repeated estimations at day care. It was generally found that they would progress to a more severe form of the disease over a period of time varying from days to weeks. If, at initial assessment, they were thought to be at high risk, with the presence of a diastolic blood pressure measurement of over 100 mmHg, elevation of uric acid, a reduced platelet count or with the presence of proteinuria, these patients were brought back to Daycare for closer monitoring. If the maternal/fetal risk was thought to very high, patients were admitted to hospital.

Overall I found that 60% of the patients referred to day care attended only once with the majority of them returning to the antenatal clinic for routine care under their referring consultant. About 20% of the patients attended day care on a regular basis for day care management because they were thought to be at high risk. A further 20% were admitted to hospital for more intensive care, either after the first Daycare attendance or after further day assessments. Therefore, the diagnosis of normality can be increased. The diagnosis of risk was still overused but greatly improved.This form of management has reduced the number of admissions and number of inpatient days spent because of hypertension. It has allowed more intensive monitoring and care to be given to patients who appear to require it.

The routine investigations of blood pressure, uric acid, platelet count, liver function tests and proteinuria were all assessed for evidence of association with each other and the outcome parameters of the pregnancy. It was found that the three measures of renal involvement were not directly related. Using multiple regression analysis, I found that proteinuria appeared to be a specific abnormality unassociated with the other parameters. It seems likely that proteinuria is a marker of 'true' preeclampsia and therefore associated with higher risk. It was also inversely associated with the delivery gestation. This implies that the earlier the gestation at presentation, the higher the incidence of proteinuria. These findings make the relevance of proteinuria difficult to assess. If present, the diagnosis is more likely to be preeclampsia and the gestation early. Both these factors will increase the risk to the fetus. The level of proteinuria does not appear to change the risk. Therefore, it would seem possible that the presence of proteinuria is associated with the pregnancies at higher risk rather than proteinuria being a risk factor itself. Hence the association of proteinuria with increased perinatal mortality (Friedman and Neff, 1975).

Uric acid was associated negatively with platelet count and positively with

abnormalities of Ast. These results suggest that elevations of uric acid are associated with general abnormalities of cellular dysfunction or damage as seen in increasing platelet consumption and elevation of Ast. Therefore, uric acid is not purely a marker of renal involvement in preeclampsia but it appears to be a reasonably accurate marker of systemic involvement. Patients with elevation of uric acid are more likely to have progressive problems and require closer monitoring. Chesley (1985) states that the presence of hyperuricaemia is important for the accuracy of the diagnosis of preeclampsia. These findings would appear to support this statement.

The results concerning serum albumin are interesting and support the idea of this being a multisystem disorder. Albumin levels will alter with changes in liver function, renal function and haemodynamic changes, particularly capillary permeability. Many of the complications of the condition can be blamed on changes in serum albumin (Cope, 1961; Brown, Zammit and Lowe, 1989; Gallery, Hunyor and Gyory, 1979). Albumin replacement has been advocated in the management of this condition (Boekkooi, Verkeste and Peeters, 1991) but it is not without hazard (Kirshon *et al.*, 1988). The factors that cause the reduction of the level of serum albumin will tend to reduce any benefit that albumin infusion will bring. It was interesting that the level of albumin was independently inversely related to the birth weight. This supports the finding that patients with oedema have larger babies (MacGillivray and Campbell, 1980). This may be due to 'oedema' of the baby secondary to reduced maternal osmolality.

The outcome of the pregnancies was related to the gestation at delivery. Babies delivered after 30 weeks did well. This would support the policy of trying to prolong the pregnancy in an attempt to improve the fetal outcome. The baby has to be in good condition before this is possible. This may also contribute to their improved outcome. Growth retardation is associated with later onset disease, not the acute onset early disease.

It was disappointing that the booking parameters did not relate strongly to the disease parameters. It has previously been suggested that the level of booking haemoglobin affects the chances of developing preeclampsia (Murphy *et al.*, 1986). There appeared to be no association between booking haemoglobin and disease severity, but there was with weight centile.

More specific investigations were also carried out into the platelet-vessel wall interaction. Three separate studies were carried out into alterations of platelet size. The first investigation was to look at platelet size throughout normal pregnancy and I showed that platelet size tended to increase in pregnancy towards term. It was therefore important when monitoring the effect of hypertension in pregnancy to use gestation matched controls as the normals, something that had not been done in

previous studies of hypertension in pregnancy and platelet size (Giles, 1981). I found that acute hypertension developing before 34 weeks was not associated with an increase of platelet size. Severe hypertension developing after 34 weeks was associated with increased platelet size, with some levels quite markedly increased above the normal level for that gestation. My conclusion from this was that patients developing preeclampsia at less than 34 weeks tend to have an acute onset disease process without any prodromal signs. On the other hand, those developing severe preeclampsia later in pregnancy would appear to have a longer disease development, which will lead to a longer stimulus to platelet activation and increased platelet turnover, leading to increasing platelet size.

In order to investigate this theory, I looked at two groups of patients thought to be at risk of worsening hypertension. One was a group of primigravidae and the other was a group of essential hypertensives. I have found that in the patients who had progressive disease they had progressing enlargement of platelet size, whereas those who remained stable had platelet size that remained within the normal range. I also showed that those whose platelet size was less than the mean of the group did not develop severe preeclampsia. These figures suggest that all the patients who developed severe disease had evidence of early platelet consumption as illustrated by a higher than average initial platelet volume and increasing platelet volume with time. In most of the patients the increasing platelet size occurred prior to the onset of the hypertension itself. This confirmed that platelet consumption is an early manifestation of the condition (Redman, Bonnar and Beilin, 1978). This progressive development of platelet consumption could be the explanation of growth retardation. If the disease presents early, there has been no chance for the platelet deposits in the placenta to cause growth problems.

Associated studies were carried out on prostacyclin levels. Again initial studies were conducted to look at the changing prostacyclin and thromboxane levels throughout pregnancy. In normal pregnancy I found the prostacyclin levels were higher in the first trimester and then fell during the third trimester,. Thromboxane fell during the second and third trimester and further in the puerperium. Studies in hypertensive patients showed that in patients with severe disease, nearly all had unrecordable levels of prostacyclin (<5 ng/ml). About 50% of those with moderate disease also had unrecordable levels, although the other 50% had levels within the normal range. Thromboxane did not appear to be elevated in patients with severe disease unless there was evidence of a large degree of platelet activity. I conclude from these studies that although the prostacyclin/thromboxane balance is disturbed it is mostly due to deficiency of prostacyclin, rather than elevations of thromboxane.

A serial study was carried out in a group of high risk primigravidae. It was

discovered that the group of patients who went on to develop hypertension in pregnancy had a higher level of prostacyclin than average, which then fell to unrecordable levels just before hypertension appeared. This suggests that there was an increased stimulus in these patients to produce prostacyclin in early pregnancy. This ability to respond appeared to be exhausted leading onto development of the hypertension itself. This suggests that there was a substance, or substances which interfered with prostacyclin production.

These studies may well agree with the studies on platelet activation. Patients who present with early disease, with sudden preeclampsia and sudden fall in platelet count, may well have absolute deficiency of prostacyclin. Those that develop severe disease over a period of time in later pregnancy initially have the ability to produce prostacyclin to protect themselves. This ability and protection slowly diminishes with time, increasing platelet consumption and leading to the development of severe preeclampsia. I feel that prostacyclin deficiency is not the underlying cause of the disease, but may well be responsible for many of the clinical manifestations seen and the patient's own ability to respond to the stimulus and the disease process. Absolute deficiency of their ability to produce prostacyclin will lead to an early onset severe disease often presenting at 28 - 30 weeks. Relative inability or an exhaustion of the ability to produce prostacyclin will tend to produce progression to severe disease over time. Thromboxane does not appear to have an early role in the disease and it is likely to be a marker of increased platelet activation.

These studies confirm the studies suggesting that there are abnormalities of platelet and prostacyclin interaction as described in Chapter 3. These have led onto the idea of using low dose aspirin as a treatment, either to prevent preeclampsia or attenuate its progress (Beaufils, Donsimoni and Colau, 1985; Wallenburg *et al.*, 1986). The logic is that aspirin will act by blocking the action of the cyclo-oxygenase enzyme system. The problem is that it will affect both prostacyclin and thromboxane production. The use of 'low dose' aspirin is an attempt to prevent this. Most of the aspirin is metabolised in the liver. This means that only the platelets in the portal circulation are affected. More work is required to elicit whether this therapy really is of benefit. There is also the concern of the effect on platelet function. If bleeding time is prolonged beyond the physiological limits, there are potential risks when using epidural cannula. The multicentre studies are awaited with interest.

In the patients who were admitted to hospital with persistent high blood pressure, I investigated the role of antihypertensive therapy. I initially looked at the acute hypertensive situation. I studied three separate medications; the standard, hydrallazine 10 mg I.M.; 200 mg oral labetalol; and 10 mg oral nicardipine. These studies showed that all three medications could adequately reduce the diastolic blood

pressure over a period of 30 minutes to 1 hour. This reduction was maintained over a period of at least 2 hours. The systolic blood pressure was not well controlled by either hydrallazine or nicardipine, but was by labetalol. These studies showed that oral medication, using either labetalol or nicardipine, is perfectly adequate in reducing blood pressure in the acute situation without resorting to parenteral drugs. This has become the standard method of treatment for patients with high blood pressure in the Glasgow Royal Maternity Hospital. If they could take oral therapy, 200 mg oral labetalol was the first line therapy.

A further randomised study was carried out using labetalol against bed rest in patients with mild to moderate disease. Because the entry criteria required the patients to have persistent hypertension after 4 days of hospital bed rest it was actually very difficult to collect the 120 patients used in the investigation. The majority of patients with mild to moderate disease did appear not to fulfil the given criteria. The results of the investigation showed that, after inclusion into the study, bed rest alone did not lower blood pressure or slow the progression of the disease. Labetalol therapy significantly reduced blood pressure and appeared to slow the progression of some of the disease parameters, assessed by blood pressure, platelet consumption and proteinuria. There was also an increased number of patients in whom blood pressure was stabilised or reduced on therapy. This is not surprising as that was the point of the therapy. There was no difference in the outcome of the pregnancies between the two groups. Since the bed rest patients were given antihypertensive therapy if their blood pressure progressed to the severe stage, it is difficult to assess the potential benefit of early intervention therapy. It would appear, however, that if patients had a diastolic blood pressure below 100 mmHg they did not benefit from early therapy. In only 30% of the patients treated with bed rest alone, did the blood pressure rise to over 100 mmHg with time. These patients could be adequately controlled with antihypertensive drugs if this was thought necessary. Therefore, patients with diastolic blood pressure between 90 and 100 mmHg were not thought to be a problem. However, they should be monitored relatively closely as outpatients. If their diastolic blood pressure rose further to above 100 mmHg, they should be admitted to hospital for closer assessment. Antihypertensive drugs should be used if this is thought necessary. There is no evidence that use of these medications causes any harm to the mother or baby. This study agrees with others in the literature that showed no apparent benefit, but did show a significant increase in the number of patients stabilised, and a reduction of progression to severe disease (Sibai *et al.*, 1987; Pickles, Symonds and Pipkin, 1989).

A further study of patients with severe hypertension was also carried out. This was a group of 186 primigravidae with diastolic blood pressures over 100 mmHg with the

presence of proteinuria of at least 0.3 g/24 hours. Long term reduction of blood pressure can be achieved in virtually all patients using either labetalol alone, or a combination of labetalol and a vasodilator, which initially was hydrallazine, but more recently was nifedipine. The average length of treatment was over 15 days. This suggests that a significant prolongation of pregnancy is possible in nearly all cases of hypertension in pregnancy. The study showed that there was no detriment to the fetal heart rate patterns or blood flow parameters as measured by Doppler velocimetry with commencement of therapy. However, a breakdown of the monitoring of the fetus showed that in looking at pregnancies presenting after 30 weeks, virtually all the babies did well, whereas the majority of the perinatal mortality occurred with presentation less than 30 weeks. This is almost completely due to the fact that after 30 weeks, if there was any sign of abnormality on fetal monitoring, delivery could be expedited. These babies now do well in modern neonatal units. In babies presenting at less than 30 weeks, there was no evidence that fetal outcome was predicted by any additional form of maternal monitoring, including uric acid, blood pressure, proteinuria, or platelet count. Poor fetal outcome was associated with evidence of fetal distress, i.e., abnormalities of fetal heart rate pattern or Doppler ultrasound abnormality or ultrasound evidence of growth retardation. Therefore, if a baby was well at presentation, lowering the blood pressure was not detrimental to fetal wellbeing. Pregnancies could be continued for approximately 2 weeks. If, on the other hand, there was evidence of fetal compromise, controlling blood pressure did not appear to improve the fetal condition. Babies may die in utero. This leads to a clinical dilemma in those patients who presented early. If they are delivered, the babies often died neonatally because of prematurity. With the improvement of the neonatal care units, these problems will further reduce. What is clear is that the fetal wellbeing is not directly related to the wellbeing of the mother. The fetus requires direct monitoring. Separate decisions are required in order to improve the outcome of the baby. Even if the results of the fetal monitoring were poor, successful outcomes were possible and the baby should rarely be 'written off'.

Over the last 9 years 3,885 hypertensive patients have been reviewed. Only 7 patients have progressed to convulsion, giving a seizure rate of 1 in 577 hypertensive patients. I do not use prophylactic anticonvulsants unless there are obvious signs of severe progressive hypertension with evidence of imminent eclampsia. These figures suggest that the incidence of eclampsia in patients with preeclampsia is very low, and therefore I feel there is no need for routine use of anticonvulsant therapy in this patient group. However, I do have available a protocol for anticonvulsant therapy in labour ward to be used by the attendant staff if it is thought necessary (Ryan, Lange

and Naugler, 1989).

In reviewing the results of these management changes, it is difficult to judge what benefits each may have brought. There is no doubt that the perinatal survival has improved over the years and now is at least as good as the rest of Scotland. Whether this is due to improved monitoring, antihypertensive usage, a specialised team, well practised protocols or a combination of some or all of these, is difficult to assess. These results do support the argument for specialist teams to manage these problems (Turnbull *et al.*, 1989).

Can a more accurate diagnosis be made?

The primigravid proteinuric hypertensive is almost certainly preeclamptic. The presence of proteinuria, hyperuricaemia and/or thrombocytopenia will increase the chances of significant disease. Intrauterine growth retardation is more likely in the presence of abnormalities of these maternal parameters. In the absence of proteinuria, hyperuricaemia or thrombocytopenia the hypertension will be almost certainly of a benign nature for both mother and baby.

11.2 Conclusions

1) A logical **stepwise** approach to the management of hypertension in pregnancy is possible.
2) The majority of patients who present with diastolics greater than 90 mmHg are of **low risk** and can be managed as outpatient without the need for intervention.
3) Patients who have blood pressures persistently greater than 100 mmHg can be treated safely with **antihypertensive therapy** as long as the baby is well.
4) Prolongation of the pregnancy is generally possible.
5) This approach was associated with a **reduction of hospital admission**, reduction of intervention and an overall **reduction in the perinatal mortality** rate associated with hypertension in pregnancy in our hospital.
6) Many of the benefits achieved are a result of the development of the **hypertensive team** and **standardised protocols** used in the stepwise management of this condition. It is felt that these could be a model for other units to follow.
7) In the absence of proteinuria, hyperuricaemia or thrombocytopenia the hypertension will be almost certainly of a **benign** nature for both mother and baby.
8) Our aetiological investigations suggest that, how a patient presents, how they progress and how severe they become, is largely dependent on the platelet-vessel wall interaction.

These abnormalities are probably mediated through the prostacyclin system. This also may relate to the vascular activity in the hypertension which then ensues. There is evidence, however, from the studies with uric acid, that there may be widespread cellular abnormalities. These may be more widespread than specifically against the platelet-vessel wall endothelium.

These studies have not established the trigger to the development of preeclampsia but have outlined the new areas of research which have developed from this work

11.3 The future.

The work in this thesis reports the completion of the studies as outlined in the previously described objectives. I now have more understanding of the disease processes, presentation and management. These studies will allow a more accurate diagnosis of preeclampsia to be made. This will allow selection of the patients at risk for further study and to reduce the intervention in those not at risk.

However, it covers only a proportion of the questions raised by the literature review and the work carried out has raised an increasing number of questions. Additional studies into areas such as genetics, immunology, haematology and membrane stability, in pregnancy hypertension, are being developed to increase, yet further, knowledge into this complex condition.

A STUDY OF AETIOLOGY, EARLY RECOGNITION, INVESTIGATION AND INTERVENTION IN HYPERTENSIVE DISEASE OF PREGNANCY

Volume II of II

by

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A Thesis Submitted for the Degree of Doctor of Medicine
to the University of Glasgow,
November, 1991

FIGURES

FIGURES

The Tables

Field	Bytes	Field	Bytes
Name	0-14	**Unit Number**	15-17
Date of Birth	18-20	**Parity**	21-22
Attendance Date	23-25	**Attendance Number**	26
LMP	27-29	**EDD**	30-32
Gestation	33	**Date of Referral**	34-36
BP at referral	37-38	**Booking BP**	39-40
Booking Gestation	41	**28 week BP**	42-43
Consultant	44	**Referred From**	45
Referred for	46	**BP's 1-5**	47-56
Dinamap BP	57-58	**Average BP**	59-60
Urea	61	**Urate**	62
Haemoglobin	63	**Platelet Count**	64
Proteinuria	65	**Cardiotocograph**	66
Fetal Heart Rate	67	**Place of Followup**	68
Date of Followup	69-71	**Diagnosis**	72

Table 2.1

A byte map of the Daycare file showing all the data that was stored and available for analysis. The data was stored in compacted format. The whole record was only 72 bytes long allowing over 3000 records stored on one floppy disc. This is the equivalent of 18 months data from Daycare.

VISIT 1 Consultant - LUNAN

Name - I NEILLY Para 0+0 Gestation 37+2 Date 18/09/89

Unit No. 134009 DOB 28/01/62 LMP 30/12/88 EDD 07/10/89

This patient was refered from the GENERAL PRACTITIONER on 13/09/89
Reason for referal was PREGNANCY HYPERTENSION. Blood pressure was 150/085

Blood pressure at 12 weeks was 110/080
Blood pressure at 28-30 weeks was 115/080

The patient was seen at Day Care on 18/09/89 5 days after referal

1) Blood Pressure -	140/080	Urea	- 2.6
2) Blood Pressure -	130/082	Urate	- 310
3) Blood Pressure -	140/085	Haemoglobin	- 12.2
4) Blood Pressure -	142/088	Platelet Count	- 240
5) Blood Pressure -	150/095	Proteinuria	- None
Average Blood Pressure -	140/086	Cardiotocograph	- REACTIVE
Dinamap Blood Pressure -	000/000	Fetal Heart Rate	- 150

The diagnosis at Day Assessment was Mild PIH
Follow up will be at DAY CARE on 22/09/89
(4 days after the Day Care attendance)

Table 2.2

The print out from the Daycare programme that is placed into the case notes. This is a false name although the data is genuine. This allows the patient's consultant to have the full monitoring information. Despite having a blood pressure of 150/95 at the antenatal clinic, this patient is clearly low risk with a low average blood pressure and normal uric acid and platelet count. The significance of these tests will be discussed later.

Diastolic	Weeks Gestation					
BP mmHg	24-27	28-32	33-34	35-36	37-38	39-41
65-74	8	7	6	4	5	5
75-84	10	8	6	6	4	3
85-94	9	9	8	6	5	5
>95	26	21	19	16	9	9

Table 3.1

Fetal loss rates per 1000 births associated with diastolic blood pressure and gestational age taken from a study of 35486 pregnancies by Friedman and Neff (1977). The increase in fetal loss rate seen in association with diastolic blood pressures above 95 mmHg was significant ($p<0.01$) in all gestations although the difference was less in gestations above 36 weeks. This is true despite the fact the numbers in the earlier gestation group are inevitably small.

		No of Women	No of Perinatal Deaths	Perinatal Mortality rate/1000
Normotensive		10787	207	19.2
Preeclampsia	**Mild**	2459	48	19.5
	Moderate	610	11	18.1
	Severe	**830**	**28**	**33.7**
Total		14686	294	20.0

Table 3.2

Data from the British Birth Survey showing that the perinatal mortality is increased only in association with severe proteinuric preeclampsia (Chamberlain *et al.*, 1978). It is important to note that even in these patients the perinatal mortality is only 175% of normal and in 96.6% of the pregnancies the fetus survived.

		Weeks Gestation					
Proteinuria	**No**	**24-27**	**28-32**	**33-34**	**35-36**	**37-38**	**39-41**
None	15365	10	10	8	6	5	4
Trace	6631	14	11	11	10	8	10
+	2712	14	6	10	16	11	6
++	597	26	**40**	**44**	17	25	**41**
+++	183	**71**	58	56	24	19	22

Table 3.3

Fetal loss rates per 1000 births associated with proteinuria **without** hypertension by gestational age taken from a study of 35486 pregnancies by Friedman and Neff (1977). The increase in fetal loss rate seen in association with proteinuria alone was seen in all gestations. The highlighted figures are significantly different ($p<0.001$). The relevance of these findings is difficult to assess. Unfortunately, the authors took a diastolic of 95 mmHg as the cut of point of hypertension. Some of these patients may have had a diastolic blood pressure of between 90 and 95 mmHg and would have been classified as severely hypertensive in many centres with the presence of proteinuria. The numbers associated with 3+'s of proteinuria were so small that the results were not statistically significant.

Diastolic BP mmHg	Proteinuria None	Trace	+	++	+++	++++	Total
<65	15.5	13.64	6.20	-	-	-	**13.60**
65-74	9.30	8.06	5.58	32.86	41.54	-	**8.84**
75-84	6.20	7.44	6.20	19.22	-	-	**6.80**
85-94	8.68	9.30	23.56†	-	22.32	-	**10.20**
95-104	19.22†	17.36†	26.66†	55.80†	115.32†	143.22†	**25.16**
105+	20.46†	27.90†	62.62†	68.82†	125.24†	110.98†	**41.48**
Total	**8.60**	**9.46**	**12.94**	**23.22**	**41.96**	**56.76**	

Table 3.4

Fetal loss rate per 1000 births by diastolic blood pressure and proteinuria. This data was taken from a study of 58906 pregnancies by Friedman and Neff (1976). The figures marked with a † are significantly increased ($p<0.01$). It can be seen that, although, each parameter appears to exert an independent influence, the diastolic blood pressure is the major factor associated with increased fetal loss.

		Preeclampsia		
		None	Mild	Proteinuric
Pregnancy	**(number)**	**%**	**%**	**%**
First	**(5124)**	71.4	23.1	5.5
Second	**(4445)**	86.1	12.5	1.4
Third	**(2726)**	88.8	9.9	1.3
Four or more	**(3060)**	88.6	10.2	1.2

Table 3.5

The percentage of patients with preeclampsia by parity. These are figures from Aberdeen quoted in MacGillivray (1983). After the first pregnancy, there appears to be a constant background incidence of both mild and proteinuric disease. Therefore, the existence of preeclampsia in parous women is possible although less likely.

	Preeclampsia		
	None	Mild	Proteinuric
Pregnancy	%	%	%
First Subsequent	74.2	21.1	4.7
Second Subsequent	88.1	10.2	0.8
Third Subsequent	92.2	7.0	0.8
Fourth Subsequent	86.7	13.3	0

Table 3.6

Incidence of preeclampsia in the subsequent four pregnancies in 128 patients with preeclampsia in their first pregnancy. These figures are from Aberdeen quoted by MacGillivray (1983). The incidence of preeclampsia appears to be higher than expected in the first subsequent pregnancy, being equal to the incidence in primigravida. After this, the incidence is no different than patients of similar parity.

		0	1	2	3
Edema		no	pretibial	generalised	
Proteinuria					
	gm%	<0.5	0.5-2	2-5	>5
	'Stix'	nil	+	++	+++
Systolic BP		<140	140-160	160-180	>180
Diastolic BP		<90	90-100	100-110	>110

Table 3.7

The definitions used by Organisation Gestosis. The patient is then classified by score such as $E_1P_2H_2$ for someone with pretibial edema, between 2-5 gm% of proteinuria and a blood pressure of 160-180/100-110 mmHg.

A. GESTATIONAL HYPERTENSION AND/OR PROTEINURIA
Hypertension and/or proteinuria developing during pregnancy, labour or the puerperium in a previously normotensive nonproteinuric women and subdivided into

1. Gestational hypertension (without proteinuria)
a) developing during pregnancy (antenatal)
b) developing for the first time in labour
c) developing for the first time in the puerperium

2) Gestational proteinuria (without hypertension)
a) developing during pregnancy (antenatal)
b) developing for the first time in labour
c) developing for the first time in the puerperium

3) Gestational proteinuric hypertension (preeclampsia)
a) developing during pregnancy (antenatal)
b) developing for the first time in labour
c) developing for the first time in the puerperium

B. CHRONIC HYPERTENSION AND CHRONIC RENAL DISEASE

Hypertension and/or proteinuria in pregnancy in a woman with chronic hypertension or chronic renal disease diagnosed either before or during or persisting after pregnancy and subdivided into

1) Chronic hypertension (without proteinuria)

2) Chronic renal disease (proteinuria and hypertension)

3) Chronic hypertension with superimposed Preeclampsia
(Proteinuria developing for the first time during pregnancy in a woman with known chronic hypertension)

C. UNCLASSIFIED HYPERTENSION AND/OR PROTEINURIA

Hypertension and/or proteinuria found after

a) at first "booking" examination after the 20th week of pregnancy (140 days) in a woman without known chronic hypertension or chronic renal disease

or

b) during pregnancy, labour or the puerperium where information is insufficient to permit classification.
is provisionally regarded as unclassified and subdivided into

1. Unclassified hypertension (without proteinuria)

2. Unclassified proteinuria (without hypertension)

3. Unclassified proteinuric hypertension (preeclampsia)

D. ECLAMPSIA
is regarded as one of the complications of the hypertensive disorders of pregnancy and should be included in a separate classification of complications.

HYPERTENSION IS DEFINED AS EITHER:
One measurement of DBP of 110 mmHg or above
Two consecutive measurements of DBP of 90 mmHg or above

PROTEINURIA DEFINED AS:
Total protein excretion of 300 mg or more in 24 hours

Table 3.8
The definitions as used by the ISSHP (Davey and MacGillivray, 1988).

	Israel	Europe America	Iraq	Asia African	Non Jews	Unknown	Total
Cases	131	216	129	173	9	75	733
Births	6464	12149	7250	20012	543	6171	32589
Rates	2.03	1.78	1.78	0.86	1.66	1.21	1.39

Table 3.9

The rates of preeclampsia in Israel, by country of origin, as found by Davies (1979). These differences may be due to many other factors, including childhood environment, as well as racial variations.

Triennium	Total Number	Rate	Preeclampsia Number	Rate	Eclampsia Number	Rate
1970-72	43	18.7	14	6.1	29	12.6
1973-75	34	17.7	15	7.8	19	9.9
1976-78	29	16.6	16	9.1	13	7.4
1979-81	36	18.7	16	8.3	20	10.4
1982-84	25	13.3	11	5.8	14	7.4
1985-87	25	12.6	13	6.5	12	6.0

Table 3.10

Number of women who died from hypertensive diseases of pregnancy and the death rate per million maternities, 1970-87 in England and Wales (DHSS, 1969, DHSS, 1974, DHSS, 1979, Turnbull *et al.*, 1989). There had been no fall in the rate of maternal death between 1970-81. The fall seen in the last two triennium is encouraging.

Causes	Eclampsia	Preeclampsia	Total
Cerebral Haemorrhage	11	13	24
Cerebral Oedema	3	1	4
Cerebral infarction	0	2	2
Cerebral Cortical necrosis	1	0	1
Cerebral softening	1	0	1
Pulmonary complication	10	4	14
Hepatic Necrosis	0	2	2
Other	0	3	3
Total	**24**	**17**	**51**

Table 3.11

The causes of the 54 maternal deaths associated with eclampsia or preeclampsia in England and Wales in years 1982-87 (Turnbull, 1987, Turnbull *et al.*, 1989). One of the patients with preeclampsia in the triennium 1982-1984 did not have a postmortem and is not included in the figures. Thirty two of the 51 patients had evidence of cerebral lesions.

	Antepartum	Intrapartum	Neonatal	Total
Timing	149	43	105	297
%	50	15	35	100
	Nonproteinuric	**Proteinuric**	**Unrecorded**	
Severity	115	132	50	297
Rate	3/1000	10/1000		6/1000

Table 3.12

Perinatal mortality related to hypertension in pregnancy in Scotland between 1977-81 (Common Services Agency., 1986). Sixty-five percent of the perinatal deaths occurred either antenatally or intrapartum. The risk of perinatal mortality for both proteinuric and nonproteinuric hypertension is well below the overall rate for the time which ranged from 18-12/1000.

Decade	Hospital	Annex	District	Total	Eclampsia	Rate /100000
33-42	32574		40995	73579	537	729†
43-52	32632		19009	51632	365	707
53-62	36606	10446	5368	52420	123	235†*
63-72	38725	18378		57103	74	130
73-82	36878	150		37028	19	51*
Total	**177406**	**28974**	**65372**	**271752**	**1118**	**411**

Table 4.1

A table of the deliveries and eclampsia over the last 50 years. The total number of deliveries were those supervised by the Glasgow Royal Maternity Hospital including those delivered in the annex and on district. The total numbers have halved since the first decade. The rate of eclampsia dramatically fell around 1950 at the time of the advent of the NHS and changes in management. There has been a further fall over the next two decades.

†Statistical difference between the rate in decades 33-42 and 53-62 ($p<0.001$)

* Statistical difference between the rate in decades 53-62 and 73-82 ($p<0.005$)

(Fishers Exact Test)

Decade	Number	Primigravida	Multigravida
33-42	537	3921 (73%)	145 (27%)
43-52	365	256 (70%)	109 (30%)
53-62	123	80 (65%)	43 (35%)
63-72	73	56 (76%)	17 (23%)
73-82	19	14 (73%)	5 (26%)
Total	**1117**	**789 (71%)**	**319 (29%)**

Table 4.2

The ratio of eclampsia in primigravida to multigravida over the 50 year period of study. The ratio has remained more or less constant (Not significant by Fishers Exact Test). Around 30% of the eclamptics are multigravida.

(Figures from the years 1933-82 in the Glasgow Royal maternity Hospital)

Decade	Number	Antenatal	Intrapartum	Postnatal
33-42	537	252 (47%)	192 (36%)	93 (17%)
43-52	365	156 (43%)	140 (38%)	69 (18%)
53-62	123	55 (45%)	37 (30%)	31 (25%)
63-72	73	26 (36%)	25 (34%)	22 (30%)
73-82	19	10 (52%)	4 (21%)	5 (26%)
Total	**1117**	**499 (44%)**	**398 (36%)**	**220 (20%)**

Table 4.3

The ratio of antenatal, intrapartum and postpartum eclamptics over the fifty years. There has been a steady decline in the numbers in each group.
(Figures from the years 1933-82 in the Glasgow Royal maternity Hospital)

Decade	Number	Antenatal	Intrapartum	Postnatal
33-52	902	408 (45%)	332 (38%)	162 (17%)
		p<0.05	**p<0.05**	**p<0.001**
53-82	215	91 (42%)	66 (31%)	58 (27%)
% reduction	**76%**	**78%**	**80%**	**64%**
Total	**1117**	**499 (44%)**	**398 (36%)**	**220 (20%)**

Table 4.4

Changes seen between the first two decades and the last three. The p values show the significance of the change. There has been a greater fall in the antenatal and intrapartum cases leading to a relative increase in postpartum cases ($p<0.001$)
(Fishers exact test)
(Figures from the years 1933-82 in the Glasgow Royal maternity Hospital)

Decade	
33-42	Delivery (Induction with bougies) Stomach and colonic lavage
43-52	Stroganoff Therapy Bromethol (IV or rectal) Morphine
53-62	Barbiturates
63-72	Diazepam Chlormethiazole
73-82	Hydrallazine Labetalol

Table 4.5

This is a list of the different treatments used over the fifty years and the decade that they were mostly used. Stomach and colonic lavage was carried out using magnesium sulphate. Stroganoff therapy was introduced in the late 1930's and was the mainstay of therapy in the early 1940's. Newer sedation agents were introduced in the later decades. Antihypertensive therapy has only been used regularly in the 1970's. These therapies represent the summary of the treatments used in all cases of eclampsias delivered in the years 1933-82 in the Glasgow Royal Maternity Hospital. Not all the consultant teams used these therapies and there were other less used therapies that were used over this period.

Decade	Number	Rate/1000 Eclamptics	Antenatal	Intrapartum	Postnatal
33-42	74	137	38 (51%)	27 (36%)	9 (13%)
43-52	44	120	25 (57%)	13 (30%)	6 (13%)
53-62	3	24	3	0	0
63-72	1	13	1	0	0
73-82	0	0	0	0	0
Total	**122**	**109**	**67 (55%)**	**40 (33%)**	**15 (12%)**

Table 4.6

The maternal deaths associated with eclampsia over the fifty year period. Overall the rate is 109/1000 eclamptics or 11%. The last maternal death associated with eclampsia occurred in 1964.

(Figures from the years 1933-82 in the Glasgow Royal maternity Hospital)

Decade	Number	Rate/1000 Eclamptics	Antenatal	Intrapartum	Postnatal
33-52	118	124	63 (53%)	40 (34%)	15 (13%)
	p<0.001				
53-82	4	37	4	0	0
Total	**122**	**109**	**67 (55%)**	**40 (33%)**	**15 (12%)**

Table 4.7

The maternal deaths associated with eclampsia, years 1933-52 compared with 1953-82. The rate has significantly reduced. (Statistical difference $p<0.001$, Fishers exact test)

(Figures from the years 1933-82 in the Glasgow Royal maternity Hospital)

Decade	Stillbirth	Neonatal Deaths	Total Deaths	Perinatal /1000 eclamptics	Perinatal /1000 deliveries
33-42	164	64	228	424	3.1
43-52	80	36	116	317	2.2
53-62	27	6	33	268	0.6
63-72	3	7	10	135	0.2
73-82	3	4	7	368	0.2
Total	**277**	**117**	**394**	**352**	**1.4**

Table 4.8

The perinatal mortality associated with eclampsia. Both the rate per 1000 deliveries in the hospital and the rate per 1000 eclamptics has steadily fallen throughout the decades. There has been an increase in the years 1973-82 but this is probably due to smaller numbers. If the last two decades are taken together, the trend is maintained (see table 4.9) This would imply that the reduction of perinatal loss related to eclampsia is due to both the reduction of the eclamptic rate and the improved survival of the babies of eclamptic mothers.

(Figures from the years 1933-82 in the Glasgow Royal maternity Hospital)

Decade	Stillbirth	Neonatal Deaths	Total Deaths	Perinatal /1000 eclamptics	Perinatal /1000 deliveries
33-62	271	106	377	367	2.1
63-82	6	11	17	182	0.2
Total	**277**	**117**	**394**	**352**	**1.4**

Table 4.9

Difference between years 1933-62 and 1963-82. The stillbirth numbers have reduced by more than the neonatal deaths resulting in a relatively higher proportion of perinatal deaths being caused by neonatal deaths compared to stillbirths ($p<0.001$). The perinatal mortality in the eclamptic group was also significantly reduced ($p<0.001$). (Fishers Exact Test)

(Figures from the years 1933-82 in the Glasgow Royal maternity Hospital)

	Number	Age	SD	Range
Primigravida	**186**	**21.5**	**4.3**	**16 - 35**
Multigravida	**115**	**26.3**	**4.9**	**18 - 40**

Table 5.1

The details of the the 186 primigravid and 115 multigravid randomly selected patients who were followed serially throughout pregnancy for the normal blood pressure changes. The Multigravida were significantly older than the primigravida ($p<0.005$) (Student's 'T' test).

Gestation	Primigravida BP SD	Multigravida BP SD	Significance
12 weeks	120.4 ± 17.0	118.0± 8.4	**NS**
	72.4 ± 11.2	71.0 ± 8.4	**NS**
16 weeks	117.3 ± 12.7	115.0± 11.9	**NS**
	69.3 ± 10.2	67.2 ± 10.2	**NS**
20 weeks	115.2 ± 16.8	111.6± 18.5	**NS**
	69.3 ± 8.8	67.7 ± 8.6	**NS**
24 weeks	116.4 ± 17.9	112.1± 11.0	**p<0.05**
	71.1 ± 9.2	65.8 ± 7.6	**p<0.001**
28 weeks	117.1 ± 17.0	113.4± 16.2	**p<0.005**
	70.6 ± 9.8	66.4 ± 7.3	**p<0.005**
30 weeks	118.3 ± 14.1	113.8± 11.5	**p<0.05**
	72.4 ± 10.2	68.7 ± 7.8	**p<0.005**
32 weeks	118.3 ± 13.2	114.3± 16.8	**p<0.05**
	72.8 ± 8.9	68.6 ± 7.3	**p<0.005**
34 weeks	118.0 ± 13.1	114.2± 16.7	**p<0.001**
	74.5 ± 11.2	70.0 ± 8.4	**p<0.001**
36 weeks	117.1 ± 16.6	114.1± 11.2	**NS**
	75.2 ± 10.8	70.1 ± 10.6	**p<0.005**
38 weeks	118.0 ± 17.0	116.4± 11.0	**NS**
	76.1 ± 11.4	70.8 ± 9.9	**p<0.001**
40 weeks	119.5 ± 11.0	119.4± 10.8	**NS**
	75.5 ± 9.0	73.8 ± 10.0	**NS**
Highest BP in Labour	118.7 ± 12.5	120.0± 15.8	**NS**
	74.0 ± 9.2	76.0 ± 10.0	**NS**
3rd day Postnatal	120.9 ± 19.4	120.7± 11.7	**NS**
	75.1 ± 11.0	76.3 ± 8.3	**NS**

Table 5.2

The mean blood pressures and standard deviations from the mean for a serial study of 186 primigravida and 115 multiparous randomly selected patients attending the antenatal clinic at the Glasgow Royal Maternity Hospital. The graph of the measurements is shown in Fig. 5.1. The previously documented fall in blood pressure in the second trimester is demonstrated with a rise to wards term (MacGillivray, Rose and Rowe, 1969). It was found that the parous women had a significantly lower systolic and diastolic blood pressure in mid-pregnancy.

	Mean	SD	Max	Min	Units
Age	22.34	4.56	28	16	Years
Booking Systolic	111.44	14.10	155	80	mmHg
Booking Diastolic	64.53	11.15	88	35	mmHg
Booking Height	160.38	6.1	180	141	cm.
Booking Weight	68.31	14.8	122	41.5	Kg.
Booking Gestation	9.74	2.27	13	6	Weeks
Booking Haemoglobin	12.8	1.0	16.4	9.6	gm/dl
Booking Hct	0.39	0.01	0.54	0.31	-

Table 6.1

The mean, standard deviation and range of the first trimester parameters of the 335 primigravida studied. The patients were studied only if they were known to be normotensive in the first trimester and developed the hypertension for the first time after 24 weeks gestation. None had any history of hypertension prior to pregnancy.

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob>F
Model	34189.7	5	6837.9	63.2	0.000
Error	40867.5	378	108.1		
Total	75057.2	383			

Coefficient of Determination (R^2)	0.5
Adjusted Coefficient (R^2)	0.4
Coefficient of Correlation (R)	0.7
Standard Error of Estimate	10.4
Durbin-Watson Statistic	1.9

Data File: Primigravida/PIH **Dependent Variable: Booking Systolic**

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob > t
Constant	50.1	16.6	3.0	0.003
Booking Diastolic	0.8	0.0	16.0	**0.000**
Booking Height	-0.0	0.1	-0.2	0.876
Booking Weight	0.1	0.0	2.3	**0.021**
Booking Haemoglobin	1.9	1.3	1.5	0.140
Booking Hct	-45.1	48.4	-0.9	0.352

Table 6.2

These tables show the results of multiple regression analysis using booking systolic blood pressure as the dependent variable compared with booking diastolic blood pressure, height, weight haemoglobin and haematocrit. This demonstrates a close **independent** relationship between the booking systolic and the booking diastolic, with lesser but significant relationship with weight. The significance of the F Ratio demonstrates that this calculation is valid. The results produce an equation suggesting that :- Systolic BP=[50+ (0.8 x Diastolic BP)+ (0.1 x weight in Kg)] mmHg

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob>F
Model	21472.1	5	4294.4	62.3	0.000
Error	26071.5	378	69.0		
Total	47543.6	383			

Coefficient of Determination (R^2)	0.5
Adjusted Coefficient (R^2)	0.4
Coefficient of Correlation (R)	0.7
Standard Error of Estimate	8.3
Durbin-Watson Statistic	1.8

Data File: Primigravida/PIHDependent Variable: Booking Diastolic

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob > t
Constant	22.0	13.3	1.6	0.100
Booking Systolic	0.5	0.0	16.0	**0.000**
Booking Height	-0.1	0.1	-1.6	0.115
Booking Weight	0.1	0.0	2.1	**0.033**
Booking Haemoglobin	-0.5	1.1	-0.4	0.655
Booking Hct	29.0	38.6	0.7	0.454

Table 6.3

These tables show the results of multiple regression analysis using booking diastolic blood pressure as the dependent variable compared with booking systolic blood pressure, height, weight, haemoglobin and haematocrit. This demonstrates a close **independent** relationship between the booking systolic and the booking diastolic, with lesser but significant relationship with weight. The significance of the F Ratio demonstrates that this calculation is valid. The results produce an equation suggesting that :- Diastolic BP=[22+ (0.5 x Systolic BP)+ (0.1 x weight in Kg)] mmHg

	Mean	SD	Max	Min	Units
Systolic	144.59	16.01	200	125	mmHg
Diastolic	99.44	9.49	140	85	mmHg
Urea	3.31	1.08	7.5	1	mmol/l
Urate	291.33	80.24	650	90	mmol/l
Haemoglobin	12.54	1.05	17.8	9.2	gm/dl
Haematocrit	0.36	0.02	0.53	0.29	-
Platelet Count	234.08	77.66	669	62	$x10^9/l$
Alkaline Phos	318.64	113.26	860	100	u/l
AST	20.82	13.83	194	6	u/l
ALT	17.19	13.91	110	6	u/l
γGT	17.67	22.03	36	3	u/l
Albumin	32.99	3.31	43	23	gm/l
Proteinuria	0.48	2.46	21.9	0	gms/24hrs
Birth Weight	3327	644	5050	690	gms
Birth Centile	56	24	>95	<5	%
Apgar 1 min	7.67	1.84	10	0	-
Apgar 5 min	9.24	1.20	10	0	-

Table 6.4

The mean and range of all parameters studied in 335 primigravida studied. For each individual patient, the results are either the last taken prior to delivery or before antihypertensive therapy was commenced. The blood pressures used were the average of four blood pressure readings taken on the day of sampling, hence the lower limit of 85 mmHg. The average birth weight and birth weight centile shows that there is no evidence of an increase incidence of growth retardation in this group. Birth weight centile was calculated using Scottish Birth centiles.

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob>F
Model	43704.7	12	3642.1	28.4	0.000
Error	38464.6	300	128.2		
Total	82169.3	312			

Coefficient of Determination (R^2)	0.5
Adjusted Coefficient (R^2)	0.5
Coefficient of Correlation (R)	0.7
Standard Error of Estimate	11.3
Durbin-Watson Statistic	1.9

Data File: Primigravida/PIHDependent Variable: Last Systolic

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob > t
Constant	46.4	22.8	2.0	0.043
Booking Systolic	0.2	0.1	3.3	**0.001**
Booking Diastolic	-0.1	0.1	-1.7	0.089
Booking Height	-0.2	0.1	-1.6	0.117
Booking Weight	0.0	o.O	1.0	0.334
Booking Haemoglobin	-1.3	1.8	-0.7	0.456
Booking Hct	25.8	65.8	0.4	0.695
Last Diastolic	1.1	0.1	14.0	**0.000**
Last Urea	0.9	0.7	1.3	0.200
Last Urate	0.0	0.0	1.1	0.289
Last Haemoglobin	-4.0	1.6	-2.4	**0.016**
Last Hct	133.6	59.8	2.2	**0.026**
Last Platelet	0.0	0.0	0.4	0.686

Table 6.5

These tables show the results of multiple regression analysis using the systolic blood pressure as the dependent variable compared with the booking parameters and the last measurements of diastolic blood pressure, urea, urate haemoglobin, haematocrit and platelet count. This demonstrates a close **independent** relationship between the last systolic and the last diastolic blood pressure readings. There was a lesser but significant relationship with the booking systolic, the last haemoglobin and last haematocrit. The relationship with haemoglobin and haematocrit is in opposite directions. There is no significant relationship with either urea, urate or platelet count.The significance of the F Ratio demonstrates that this calculation is valid.

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob>F
Model	16716.6	12	1393.0	32.1	0.000
Error	13003.2	300	43.3		
Total	29719.8	312			

Coefficient of Determination (R^2)	0.6
Adjusted Coefficient (R^2)	0.5
Coefficient of Correlation (R)	0.7
Standard Error of Estimate	6.6
Durbin-Watson Statistic	2.0

Data File: Primigravida/PIHDependent Variable: Last Diastolic

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob > t
Constant	39.0	13.2	3.0	0.003
Booking Systolic	-0.1	0.0	-2.0	0.050
Booking Diastolic	0.1	0.0	2.9	**0.004**
Booking Height	-0.0	0.1	-0.2	0.880
Booking Weight	0.0	0.0	0.5	0.612
Booking Haemoglobin	0.3	1.0	0.3	0.766
Booking Hct	-9.9	38.3	-0.3	0.796
Last Systolic	0.4	0.0	14.0	0.000
Last Urea	1.0	0.4	2.5	**0.013**
Last Urate	0.0	0.0	2.2	**0.029**
Last Haemoglobin	2.1	1.0	2.2	**0.029**
Last Hct	-59.2	34.9	-1.7	0.090
Last Platelet	-0.0	0.0	-2.7	**0.007**

Table 6.6

These tables show the results of multiple regression analysis using the diastolic blood pressure as the dependent variable compared with the booking parameters and the last systolic blood pressure, urea, urate, haemoglobin, haematocrit and platelet count. This demonstrates a close **independent** relationship between the last diastolic and the last systolic blood pressure readings. There is a lesser but significant relationship with the booking diastolic. the last urea, urate, haemoglobin and platelet count. There is no significant relationship with haematocrit. The significance of the F Ratio demonstrates that this calculation is valid.

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob>F
Model	145.2	18	8.1	8.9	0.000
Error	252.1	277	0.9		
Total	397.3	295			

Coefficient of Determination (R^2)	0.4
Adjusted Coefficient (R^2)	0.3
Coefficient of Correlation (R)	0.6
Standard Error of Estimate	1.0
Durbin-Watson Statistic	1.8

Data File: Primigravida/PIHDependent Variable: Last Urea

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob > t
Constant	-3.0	2.1	-1.4	0.157
Booking Systolic	0.0	0.0	0.1	0.923
Booking Diastolic	-0.0	0.0	-1.0	0.300
Booking Height	0.0	0.0	1.3	0.187
Booking Weight	-0.0	0.0	-1.3	0.182
Booking Haemoglobin	-0.3	0.2	-2.1	**0.041**
Booking Hct	10.9	6.0	1.8	0.069
Last Systolic	0.0	0.0	1.7	0.098
Last Diastolic	0.0	0.0	1.6	0.105
Last Urate	0.0	0.0	6.7	**0.000**
Last Haemoglobin	0.0	0.1	0.0	0.973
Last Hct	0.7	5.3	0.1	0.888
Last Platelet	0.0	0.0	0.6	0.560
Last Alk Phos	0.0	0.0	0.1	0.921
Last Ast	-0.0	0.0	-1.6	0.111
Last Alt	0.0	0.0	2.4	**0.019**
Last γGT	0.0	0.0	1.0	0.333
Last Albumin	0.0	0.0	0.6	0.548
Last Proteinuria	0.0	0.0	1.3	0.212

Table 6.7

These tables show the results of multiple regression analysis using urea as the dependent variable. This demonstrates a close **independent** relationship between the last urea and the uric acid. There is a lesser but significant relationship with the booking haemoglobin and last Alt. There is no significant relationship with any of the other parameters. This would imply that renal impairment, as measured by urea level, is not related to the markers of disease activity. The significance of the F Ratio demonstrates that this calculation is valid.

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob>F
Model	988739.0	17	58161.1	14.3	0.000
Error	1133506.5	278	4077.4		
Total	2122245.5	295			

Coefficient of Determination (R^2)	0.5
Adjusted Coefficient (R^2)	0.4
Coefficient of Correlation (R)	0.7
Standard Error of Estimate	63.9
Durbin-Watson Statistic	2.1

Data File: Primigravida/PIHDependent Variable: Last Urate

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob > t
Constant	405.7	138.5	2.9	0.004
Booking Systolic	0.2	0.4	0.5	0.635
Booking Diastolic	-0.6	0.5	-1.3	0.193
Booking Height	-0.0	0.7	-0.1	0.954
Booking Weight	0.0	0.3	0.1	0.931
Booking Haemoglobin	1.4	10.8	0.1	0.895
Booking Hct	-321.3	401.4	-0.8	0.424
Last Systolic	0.2	0.3	0.5	0.625
Last Diastolic	1.2	0.6	2.2	**0.031**
Last Urea	25.1	3.7	6.7	**0.000**
Last Haemoglobin	3.5	9.5	0.4	0.711
Last Hct	-113.7	351.7	-0.3	0.747
Last Platelet	-0.1	0.1	-1.8	0.066
Last Alk Phos	0.1	0.0	1.7	0.083
Last Ast	1.2	0.5	2.6	**0.009**
Last Alt	-0.5	0.5	-1.0	0.309
Last γGT	0.6	0.4	1.5	0.124
Last Albumin	-6.8	1.3	-5.3	**0.000**
Last Proteinuria	-1.0	1.6	-0.6	0.519

Table 6.8

These tables show the results of multiple regression analysis using urate as the dependent variable. This demonstrates a close **independent** relationship between the last urate and urea. There is no relationship with any of the booking parameters. There is a significant relationship with the last diastolic, platelet count and albumin, all recognised markers of disease severity. There is also a significant relationship to Ast. This suggests that changes in Ast, unlike Alt, are more directly related to the disease process. The significance of the F Ratio demonstrates that this calculation is valid.

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob>F
Model	498.7	18	27.7	4.6	0.000
Error	1676.5	277	6.1		
Total	2175.2	295			

Coefficient of Determination (R^2)	0.2
Adjusted Coefficient (R^2)	0.2
Coefficient of Correlation (R)	0.5
Standard Error of Estimate	2.5
Durbin-Watson Statistic	2.1

Data File: Primigravida/PIHDependent Variable: Last Proteinuria

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob> t
Constant	4.8	5.5	0.9	0.382
Booking Systolic	-0.0	0.0	-0.1	0.894
Booking Diastolic	-0.0	0.0	-0.3	0.771
Booking Height	0.0	0.0	0.6	0.522
Booking Weight	-0.0	0.0	-0.8	0.415
Booking Haemoglobin	-1.1	0.4	-2.6	**0.010**
Booking Hct	29.4	15.4	1.9	0.058
Last Systolic	0.0	0.0	1.2	0.244
Last Diastolic	0.0	0.0	1.5	0.142
Last Urea	0.2	0.2	1.3	0.212
Last Urate	-0.0	0.0	-0.5	0.608
Last Haemoglobin	0.2	0.4	0.5	0.598
Last Hct	-4.7	13.6	-0.3	0.729
Last Platelet	-0.0	0.0	-0.5	0.620
Last Alk Phos	-0.0	0.0	-1.2	0.227
Last Ast	-0.0	0.0	-0.5	0.610
Last Alt	0.0	0.0	0.5	0.613
Last γGT	-0.0	0.0	-0.3	0.728
Last Albumin	-0.3	0.1	-5.0	**0.000**

Table 6.9

These tables show the results of multiple regression analysis using proteinuria as the dependent variable. This demonstrates a close **independent** negative relationship between the last proteinuria and albumin. Apart from a relationship with the booking haemoglobin, there is no independent relationship with any other parameter. This suggests that proteinuria is due to a specific abnormality independent of the rest of the disease process. The significance of the F Ratio demonstrates that this calculation is valid.

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob>F
Model	279.1	17	16.4	101.0	0.000
Error	46.0	283	0.2		
Total	325.2	300			

Coefficient of Determination (R^2)	0.9
Adjusted Coefficient (R^2)	0.8
Coefficient of Correlation (R)	0.9
Standard Error of Estimate	0.4
Durbin-Watson Statistic	2.0

Data File: Primigravida/PIHDependent Variable: Last Haemoglobin

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob > t
Constant	-0.3	0.6	-0.5	0.599
Booking Systolic	0.0	0.0	0.8	0.453
Booking Diastolic	-0.0	0.0	-0.9	0.345
Booking Height	0.0	0.0	1.3	0.302
Booking Weight	0.0	0.0	0.5	0.589
Booking Haemoglobin	0.2	0.1	3.2	**0.002**
Booking Hct	-5.3	2.5	-2.1	**0.035**
Last Systolic	-0.0	0.0	-2.3	**0.020**
Last Diastolic	0.0	0.0	2.1	**0.034**
Last Urea	-0.0	0.0	-0.1	0.913
Last Urate	0.0	0.0	0.4	0.685
Last Hct	33.4	1.0	34.4	**0.000**
Last Platelet	-0.0	0.0	-0.6	0.575
Last Alk Phos	-0.0	0.0	-1.2	0.250
Last Ast	0.0	0.0	0.2	0.854
Last Alt	-0.0	0.0	-0.2	0.876
Last γGT	0.0	0.0	0.6	0.568
Last Albumin	-0.0	0.0	-1.0	0.316
Last Proteinuria	0.0	0.0	0.4	0.678

Table 6.10

These tables show the results of multiple regression analysis using haemoglobin as the dependent variable. This demonstrates a close **independent** relationship between the last haemoglobin and the booking haemoglobin and haematocrit, both the systolic and diastolic blood pressure, and the last haematocrit. There is no independent relationship with any other parameter. The significance of the F Ratio demonstrates that this calculation is valid.

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob>F
Model	0.2	18	0.0	92.3	0.000
Error	0.0	277	0.0		
Total	0.2	295			

Coefficient of Determination (R^2)	0.9
Adjusted Coefficient (R^2)	0.8
Coefficient of Correlation (R)	0.9
Standard Error of Estimate	0.0
Durbin-Watson Statistic	2.0

Data File: Primigravida/PIH **Dependent Variable: Last Hct**

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob > t
Constant	0.0	0.0	0.6	0.541
Booking Systolic	-0.0	0.0	-0.6	0.542
Booking Diastolic	0.0	0.0	1.0	0.339
Booking Height	0.0	0.0	1.1	0.266
Booking Weight	-0.0	0.0	-1.1	0.262
Booking Haemoglobin	-0.0	0.0	-2.5	**0.013**
Booking Hct	0.2	0.1	2.8	**0.005**
Last Systolic	0.0	0.0	2.6	**0.010**
Last Diastolic	-0.0	0.0	-1.8	0.078
Last Urea	0.0	0.0	0.1	0.888
Last Urate	-0.0	0.0	-0.5	0.624
Last Haemoglobin	0.0	0.0	34.3	**0.000**
Last Platelet	-0.0	0.0	-0.6	0.560
Last Alk Phos	0.0	0.0	1.6	0.100
Last Ast	0.0	0.0	0.0	0.986
Last Alt	-0.0	0.0	-0.3	0.748
Last γGT	0.0	0.0	0.3	0.786
Last Albumin	0.0	0.0	2.1	**0.039**
Last Proteinuria	-0.0	0.0	-0.3	0.729

Table 6.11

These tables show the results of multiple regression analysis using haematocrit as the dependent variable. This demonstrates a close **independent** relationship between the last haematocrit and the booking haemoglobin and haematocrit, the systolic blood pressure, the last haemoglobin and the last albumin. There is no independent relationship with any other parameter. The significance of the F Ratio demonstrates that this calculation is valid.

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob>F
Model	404712.3	18	22484.0	4.2	0.000
Error	1482319.6	277	5351.3		
Total	1887031.9	295			

Coefficient of Determination (R^2)	0.2
Adjusted Coefficient (R^2)	0.2
Coefficient of Correlation (R)	0.5
Standard Error of Estimate	73.2
Durbin-Watson Statistic	1.8

Data File: Primigravida/PIH **Dependent Variable: Last Platelet Count**

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob > t
Constant	709.0	157.3	4.5	o.000
Booking Systolic	-0.7	0.4	-1.7	0.082
Booking Diastolic	0.2	0.5	0.5	0.652
Booking Height	-1.2	0.8	-1.6	0.115
Booking Weight	0.7	0.3	2.3	**0.024**
Booking Haemoglobin	0.4	12.4	0.0	0.971
Booking Hct	89.9	461.7	0.2	0.846
Last Systolic	0.2	0.4	0.6	0.568
Last Diastolic	-1.8	0.7	-2.7	**0.007**
Last Urea	2.7	4.6	0.6	0.560
Last Urate	-0.1	0.1	-1.9	0.053
Last Haemoglobin	-7.3	10.9	-0.7	0.503
Last Hct	-235.9	404.7	-0.6	0.560
Last Alk Phos	0.0	0.0	1.2	0.249
Last Ast	-1.3	0.5	-2.4	**0.018**
Last Alt	0.3	0.6	0.5	0.613
Last γGT	-0.1	0.4	-0.2	0.815
Last Albumin	2.2	1.6	1.4	0.169
Last Proteinuria	-0.9	1.8	-0.5	0.620

Table 6.12

These tables show the results of multiple regression analysis using the platelet count as the dependent variable. This demonstrates a close **independent** relationship between the last platelet count and the booking weight, the diastolic blood pressure, and the last Ast. There is no independent relationship with any other parameter including the systolic blood pressure. The significance of the F Ratio demonstrates that this calculation is valid.

Normal = No further blood pressures greater than 90 mmHg
Mild = Blood pressures never going above 100 mmHg
Moderate = Blood pressures between 100 and 109 mmHg
Severe = Blood pressures ≥ 110 mmHg
or the presence of proteinuria.

Table 6.13
Definitions used in the followup of patients in the prediction study shown in the next 4 tables.

	Long Term Outcome				
Daycare Diastolic	**Number**	**Normal**	**Mild**	**Moderate**	**Severe**
<90	846	293	434	109	10
90-100	197	0	33	98	66
>100	44	0	0	11	33
Total	**1087**	**293**	**467**	**218**	**109**

Table 6.14

The long term outcome compared with the average Daycare diastolic blood pressure of 1087 consecutive Primigravida attending Daycare for the first time after 24 weeks. As will be discuss in Chapter 7, most patients had normal blood pressure.

Daycare Uric acid	Number	Long Term Outcome Normal	Mild	Moderate	Severe
<250	153	109	22	22	0
250-370	782	184	442	120	36
>370	152	0	3	76	73
Total	**1087**	**293**	**467**	**218**	**109**

Table 6.15

The long term outcome compared with the Daycare uric acid level in 1087 consecutive Primigravida attending Daycare for the first time after 24 weeks. It would appear that in this group of patients a level of 370 mmol/l is too high to be the upper limit of normality as few patients have a level above this.

		Long Term Outcome			
Daycare Platelets	**Number**	**Normal**	**Mild**	**Moderate**	**Severe**
>250	489	217	228	44	0
150-250	550	76	228	163	83
<150	48	0	11	11	26
Total	**1087**	**293**	**467**	**218**	**109**

Table 6.16

The long term outcome compared with the platelet count in 1087 consecutive Primigravida attending Daycare for the first time after 24 weeks. It would appear that in this group of patients a level of 150 $x10^9$/ml is too low to be the lower limit of normality as few patients have a level below this.

Daycare	Long Term Outcome				
	Number	**Normal**	**Mild**	**Moderate**	**Severe**
Diastolic <90	846	293	434	109	10
and Urate <350	630	281	276	65	8
and Platelets >200	537	264	245	22	6

Table 6.17

The long term outcome compared with the combination of results obtained at the first Daycare appointment. The cutoff levels were chosen as the best compromise of selectivity and specificity of diagnosis. Less than 50% of the patients had normal levels of all three parameters but these did well.

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob>F
Model	1387873.8	18	77104.1	4.6	0.000
Error	4637996.7	277	16743.7		
Total	6025870.5	295			

Coefficient of Determination (R^2)	0.2
Adjusted Coefficient (R^2)	0.2
Coefficient of Correlation (R)	0.5
Standard Error of Estimate	129.4
Durbin-Watson Statistic	2.1

Data File: Primigravida/PIH **Dependent Variable: Last Alk Phos**

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob > t
Constant	715.8	285.0	2.5	0.013
Booking Systolic	-0.3	0.8	-0.4	0.671
Booking Diastolic	-1.5	o.9	-1.7	0.092
Booking Height	-1.9	1.3	-1.4	0.151
Booking Weight	-0.2	0.6	-0.4	0.668
Booking Haemoglobin	24.1	21.9	1.1	0.273
Booking Hct	-1034.7	814.4	-1.3	0.205
Last Systolic	-0.1	0.7	-0.1	0.928
Last Diastolic	1.8	1.2	1.5	0.126
Last Urea	0.8	8.1	0.1	0.921
Last Urate	0.2	0.1	1.7	0.083
Last Haemoglobin	-24.0	19.2	-1.2	0.214
Last Hct	1174.9	712.8	1.6	0.100
Last Platelet	0.1	0.1	1.2	0.249
Last Ast	-0.2	0.9	-0.2	0.829
Last Alt	-0.2	1.0	-0.2	0.842
Last γGT	3.2	0.8	4.2	**0.000**
Last Albumin	-8.5	2.8	-3.1	**0.002**
Last Proteinuria	-3.8	3.2	-1.2	0.227

Table 6.18

These tables show the results of multiple regression analysis using alkaline phosphatase as the dependent variable. This demonstrates the close **independent** relationship between the last alkaline phosphatase and both the last γGT and the last albumin. There is no significant relationship with any of the other parameters. The significance of the F Ratio demonstrates that this calculation is valid.9

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob>F
Model	34683.7	17	2040.2	32.4	0.000
Error	17635.1	280	63.0		
Total	52318.8	297			

Coefficient of Determination (R^2)	0.7
Adjusted Coefficient (R^2)	0.6
Coefficient of Correlation (R)	0.8
Standard Error of Estimate	7.9
Durbin-Watson Statistic	2.1

Data File: Primigravida/PIH **Dependent Variable: Last Alt**

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob > t
Constant	-27.8	17.1	-1.6	0.105
Booking Systolic	-0.0	0.0	-0.4	0.672
Booking Diastolic	0.1	0.1	1.8	0.076
Booking Height	0.1	0.1	0.8	0.412
Booking Weight	0.0	0.0	0.6	0.516
Booking Haemoglobin	1.1	o.5	2.0	**0.042**
Last Systolic	-0.0	0.0	-0.0	0.982
Last Diastolic	-0.0	0.1	-0.7	0.493
Last Urea	1.3	0.5	2.6	**0.011**
Last Urate	-0.0	0.0	-1.1	0.287
Last Haemoglobin	-0.2	1.2	-0.2	0.867
Last Hct	-1.6	43.0	-0.0	0.971
Last Platelet	0.0	0.0	0.5	0.601
Last Alk Phos	-0.0	0.0	-0.3	0.740
Last Ast	0.7	0.0	18.6	**0.000**
Last γGT	0.2	0.0	5.3	**0.000**
Last Albumin	0.0	0.2	0.1	0.890
Last Proteinuria	0.1	0.2	0.7	0.488

Table 6.19

These tables show the results of multiple regression analysis using Alt as the dependent variable. This demonstrates the close **independent** relationship between the last Ast, the last urea and the last GT. There a lesser relationship with the booking haemoglobin. There is no significant relationship with any of the other parameters. The significance of the F Ratio demonstrates that this calculation is valid.

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob>F
Model	34105.3	18	1894.7	28.0	0.000
Error	18771.5	277	67.8		
Total	52876.8	295			

Coefficient of Determination (R^2)	0.6
Adjusted Coefficient (R^2)	0.6
Coefficient of Correlation (R)	0.8
Standard Error of Estimate	8.2
Durbin-Watson Statistic	2.1

Data File: Primigravida/PIH **Dependent Variable: Last Ast**

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob > t
Constant	31.2	18.2	1.7	0.089
Booking Systolic	-0.0	0.0	-0.5	0.599
Booking Diastolic	-0.0	0.1	-0.8	0.419
Booking Height	-0.0	0.1	-0.1	0.902
Booking Weight	-0.0	0.0	-0.2	0.844
Booking Haemoglobin	1.7	1.4	1.3	0.211
Booking Hct	-92.7	51.7	-1.8	0.074
Last Systolic	0.0	0.0	0.3	0.799
Last Diastolic	0.0	0.1	0.2	0.850
Last Urea	-0.8	0.5	-1.6	0.111
Last Urate	0.0	0.0	2.6	**0.009**
Last Haemoglobin	-0.0	1.2	-0.0	0.968
Last Hct	0.8	45.6	0.0	0.986
Last Platelet	-0.0	0.0	-2.4	**0.018**
Last Alk Phos	-0.0	0.0	-0.2	0.829
Last Alt	0.8	0.0	18.6	**0.000**
Last γGT	-0.0	0.0	-1.0	0.319
Last Albumin	-0.1	0.2	-0.6	0.527
Proteinuria	-0.1	0.2	-0.5	0.610

Table 6.20

These tables show the results of multiple regression analysis using Ast as the dependent variable. This demonstrates the close **independent** relationship between the last Ast and the last uric acid, the last platelet count and the last Alt. There is no significant relationship with any of the other parameters. The significance of the F Ratio demonstrates that this calculation is valid.

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob>F
Model	11826.0	18	657.0	6.6	0.000
Error	27417.0	277	99.0		
Total	39243.0	295			

Coefficient of Determination (R^2)	0.3
Adjusted Coefficient (R^2)	0.3
Coefficient of Correlation (R)	0.5
Standard Error of Estimate	9.9
Durbin-Watson Statistic	2.0

Data File: Primigravida/PIHDependent Variable: Last γGT

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob > t
Constant	45.1	22.0	2.1	0.041
Booking Systolic	0.0	0.1	0.4	0.718
Booking Diastolic	-0.1	0.1	-0.8	0.408
Booking Height	-0.3	0.1	-3.0	**0.003**
Booking Weight	0.1	0.0	1.4	0.166
Booking Haemoglobin	-0.5	1.7	-o.3	0.788
Booking Hct	-12.0	62.8	-0.2	0.848
Last Systolic	-0.1	0.1	-1.8	0.075
Last Diastolic	0.1	0.1	1.0	0.315
Last Urea	0.6	0.6	1.0	0.333
Last Urate	0.0	0.0	1.1	0.294
Last Haemoglobin	0.6	1.5	0.4	0.668
Last Hct	15.0	55.1	0.3	0.786
Last Platelet	-0.0	0.0	-0.2	0.815
Last Alk Phos	0.0	0.0	4.2	**0.000**
Last Ast	-0.1	0.1	-1.0	0.319
Last Alt	0.4	0.1	5.2	**0.000**
Last Albumin	0.1	0.2	0.7	0.495
Last Proteinuria	-0.1	0.2	-0.3	0.728

Table 6.21

These tables show the results of multiple regression analysis using γGT as the dependent variable. This demonstrates the close **independent** relationship between the last γGT and the last alk phos and the last Alt. There is also a relationship with the booking height. There is no significant relationship with any of the other parameters. The significance of the F Ratio demonstrates that this calculation is valid.

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob>F
Model	1134.9	18	63.1	8.2	0.000
Error	2133.2	277	7.7		
Total	3268.2	295			

Coefficient of Determination (R^2)	0.3
Adjusted Coefficient (R^2)	0.3
Coefficient of Correlation (R)	0.6
Standard Error of Estimate	2.8
Durbin-Watson Statistic	2.0

Data File: Primigravida/PIHDependent Variable: Last Albumin

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob > t
Constant	28.1	5.9	4.7	0.000
Booking Systolic	0.0	0.0	1.1	0.291
Booking Diastolic	-0.0	0.0	-1.6	0.111
Booking Height	0.1	0.0	1.9	0.054
Booking Weight	-0.0	0.0	-0.5	0.592
Booking Haemoglobin	0.2	0.5	0.3	0.732
Booking Hct	-16.0	17.5	-0.9	0.362
Last Systolic	-0.0	0.0	-1.3	0.186
Last Diastolic	0.0	0.0	0.3	0.752
Last Urea	0.1	0.2	0.6	0.548
Last Urate	-0.0	0.0	-4.8	**0.000**
Last Haemoglobin	-0.4	0.4	-1.0	0.330
Last Hct	31.6	15.2	2.1	**0.039**
Last Platelet	0.0	0.0	1.4	0.169
Last Alk Phos	-0.0	0.0	-3.1	**0.002**
Last Ast	-0.0	0.0	-0.6	0.527
Last Alt	0.0	0.0	0.2	0.819
Last γGT	0.0	0.0	0.7	0.495
Last Proteinuria	-0.3	0.1	-5.0	**0.000**

Table 6.22

These tables show the results of multiple regression analysis using albumin as the dependent variable. This demonstrates the close **independent** relationship between the last albumin and the last urate, haematocrit, alkaline phosphatase and negatively with the last proteinuria. There is no significant relationship with any of the other parameters. The significance of the F Ratio demonstrates that this calculation is valid.

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob>F
Model	395.2	19	20.8	6.9	0.000
Error	826.1	275	3.0		
Total	1221.3	294			

Coefficient of Determination (R^2)	0.3
Adjusted Coefficient (R^2)	0.3
Coefficient of Correlation (R)	0.6
Standard Error of Estimate	1.7
Durbin-Watson Statistic	2.0

Data File: Primigravida/PIH **Dependent Variable: Delivery Gestation**

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob > t
Constant	37.4	3.9	9.7	0.000
Booking Systolic	-0.0	0.0	-0.4	0.694
Booking Diastolic	-0.0	0.0	-0.8	0.448
Booking Height	0.0	0.0	1.6	0.104
Booking Weight	-0.0	0.0	-0.9	0.396
Booking Haemoglobin	0.5	0.3	1.7	0.097
Booking Hct	-8.1	10.9	-0.7	0.460
Last Systolic	-0.0	0.0	-1.6	0.102
Last Diastolic	-0.0	0.0	-0.6	0.535
Last Urea	-0.3	0.1	-3.2	**0.002**
Last Urate	0.0	0.0	0.7	0.454
Last Haemoglobin	-0.1	0.3	-0.4	0.688
Last Hct	-4.7	9.6	-0.5	0.627
Last Platelet	0.0	0.0	2.2	**0.031**
Last Alk Phos	-0.0	0.0	-0.9	0.379
Last Ast	-0.0	0.0	-0.7	0.508
Last Alt	0.0	0.0	0.4	0.678
Last γGT	-0.0	0.0	-0.8	0.445
Last Albumin	0.1	0.0	1.4	0.151
Last Proteinuria	-0.2	0.0	-3.6	**0.000**

Table 6.23

These tables show the results of multiple regression analysis using the delivery gestation as the dependent variable. This demonstrates the close **independent** relationship between the delivery gestation and the last urea, platelet count and the last proteinuria. There is no significant relationship with any of the other parameters. The significance of the F Ratio demonstrates that this calculation is valid.

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob>F
Model	61416214.6	20	3070810.7	14.6	0.000
Error	56025446.2	267	209833.1		
Total	117441660.8	287			

Coefficient of Determination (R^2)	0.5
Adjusted Coefficient (R^2)	0.5
Coefficient of Correlation (R)	0.7
Standard Error of Estimate	458.1
Durbin-Watson Statistic	1.8

Data File: Primigravida/PIH **Dependent Variable: Birth Weight**

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob > t
Constant	-4952.4	1237.6	-4.0	0.000
Booking Systolic	1.2	2.7	0.4	0.662
Booking Diastolic	3.0	3.3	0.9	0.374
Booking Height	18.o	4.8	3.7	**0.000**
Booking Weight	6.1	2.1	2.9	**0.003**
Booking Haemoglobin	85.1	79.4	1.1	0.284
Booking Hct	-1762.9	2936.0	-0.6	0.549
Last Systolic	1.7	2.5	0.7	0.506
Last Diastolic	-8.2	4.3	-1.9	0.055
Last Urea	-69.6	29.8	-2.3	**0.020**
Last Urate	0.3	0.4	0.7	0.473
Last Haemoglobin	-42.6	69.8	-0.6	0.542
Last Hct	-12.0	2598.9	-0.0	0.996
Last Platelet	-0.3	0.4	-0.8	0.414
Last Alk Phos	-0.5	0.2	-2.2	**0.030**
Last Ast	0.9	3.4	0.3	0.786
Last Alt	-2.5	3.5	-0.7	0.470
Last γGT	-0.6	2.9	-0.2	0.838
Last Albumin	-29.4	10.0	-2.9	**0.004**
Last Proteinuria	-22.7	11.8	-1.9	0.055
Delivery Gestation	171.3	17.5	9.8	**0.000**

Table 6.24

These tables show the results of multiple regression analysis using the birth weight as the dependent variable. This demonstrates the close **independent** relationship between the birth weight and the delivery gestation as would be expected. There is also a relationship with the booking height and weight, last urea, alk phos and albumin. There is no significant relationship with any of the other parameters. The significance of the F Ratio demonstrates that this calculation is valid.

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob>
Model	159770.4	21	7608.1	135.6	0.000
Error	14924.3	266	56.1		
Total	174694.7	287			

Coefficient of Determination (R^2)	0.9
Adjusted Coefficient (R^2)	0.9
Coefficient of Correlation (R)	1.0
Standard Error of Estimate	7.5
Durbin-Watson Statistic	2.1

Data File: Primigravida/PIH **Dependent Variable: Weight Centile**

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob > t
Constant	301.4	20.8	14.5	0.000
Booking Systolic	0.1	0.0	1.4	0.154
Booking Diastolic	-o.1	0.1	-1.7	0.090
Booking Height	-0.0	0.1	-0.5	0.597
Booking Weight	-0.0	0.0	-0.2	0.819
Booking Haemoglobin	-3.9	1.3	-3.0	**0.003**
Booking Hct	129.6	48.0	2.7	**0.007**
Last Systolic	-0.0	0.0	-0.0	0.982
Last Diastolic	0.0	0.1	0.0	0.979
Last Urea	-0.4	0.5	-0.9	0.373
Last Urate	0.0	0.0	1.3	0.189
Last Haemoglobin	0.4	1.1	0.4	0.721
Last Hct	-31.2	42.5	-0.7	0.463
Last Platelet	0.0	0.0	0.3	0.749
Last Alk Phos	-0.0	0.0	-1.3	0.194
Last Ast	0.0	0.1	0.5	0.596
Last Alt	-0.1	0.1	-1.1	0.277
Last γGT	-0.0	0.0	-0.6	0.546
Last Albumin	-0.1	0.2	-0.3	0.729
Last Proteinuria	0.1	0.2	0.4	0.695
Delivery Gestation	-9.9	0.3	-29.5	**0.000**
Birth Weight	0.0	0.0	46.5	**0.000**

Table 6.25

These tables show the results of multiple regression analysis using the weight centile as the dependent variable. The weight centiles were worked out for the Scottish tables of weight centiles. This demonstrates the close **independent** relationship between the weight centile and the booking haemoglobin and haematocrit, and the delivery gestation and birth weight. There is no significant relationship with any of the other parameters. The significance of the F Ratio demonstrates that this calculation is valid.

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob,
Model	274.6	22	12.5	4.1	0.000
Error	815.3	265	3.1		
Total	1089.9	287			

Coefficient of Determination (R^2)	0.3
Adjusted Coefficient (R^2)	0.2
Coefficient of Correlation (R)	0.5
Standard Error of Estimate	1.8
Durbin-Watson Statistic	1.8

Data File: Primigravida/PIH **Dependent Variable: Apgar 1 Minute**

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob > t
Constant	-25.2	6.5	-3.9	0.000
Booking Systolic	-0.0	0.0	-0.3	0.760
Booking Diastolic	0.0	0.0	0.3	0.770
Booking Height	0.0	0.0	1.1	0.292
Booking Weight	-0.0	0.0	-0.8	0.419
Booking Haemoglobin	0.3	0.3	0.8	0.412
Booking Hct	4.0	11.4	0.3	0.727
Last Systolic	0.0	0.0	0.8	0.434
Last Diastolic	-0.0	0.0	-0.9	0.350
Last Urea	-0.4	0.1	-3.4	**0.001**
Last Urate	0.0	0.0	1.8	0.066
Last Haemoglobin	0.0	0.3	0.1	0.909
Last Hct	-4.1	10.0	-0.4	0.681
Last Platelet	0.0	0.0	1.0	0.325
Last Alk Phos	-0.0	0.0	-0.7	0.472
Last Ast	-0.0	0.0	-1.9	0.058
Last Alt	0.0	0.0	1.8	0.074
Last γGT	0.0	0.0	1.1	0.283
Last Albumin	-0.0	0.0	-0.9	0.349
Last Proteinuria	0.1	0.0	1.4	0.152
Delivery Gestation	0.9	0.2	5.4	**0.000**
Birth Weight	-0.0	0.0	-3.8	**0.000**
Weight Centile	0.1	0.0	4.1	**0.000**

Table 6.26

These tables show the results of multiple regression analysis using the Apgar at minute as the dependent variable. This demonstrates the close **independent** relationship between the Apgar at 1 minute and the last urea, delivery gestation, birth weight and weight centile. There is no significant relationship with any of the other parameters. The significance of the F Ratio demonstrates that this calculation is valid.

Data File: Primigravida/PIH

Source	Sum of Squares	Deg. of Freedom	Mean Squares	F-Ratio	Prob>F
Model	211.9	23	9.2	11.5	0.000
Error	211.0	264	0.8		
Total	422.9	287			

Coefficient of Determination (R^2)	0.5
Adjusted Coefficient (R^2)	0.5
Coefficient of Correlation (R)	0.7
Standard Error of Estimate	0.9
Durbin-Watson Statistic	2.1

Data File: Primigravida/PIH **Dependent Variable: Apgar 5 Minute**

Variable Name	Coefficient	Std. Err. Estimate	t Statistic	Prob, t
Constant	3.4	3.4	1.0	0.318
Booking Systolic	0.0	0.0	1.4	0.152
Booking Diastolic	-0.0	0.0	-1.2	0.218
Booking Height	-0.0	0.0	-0.3	0.768
Booking Weight	-0.0	0.0	-0.1	0.956
Booking Haemoglobin	-0.1	0.2	-0.8	0.443
Booking Hct	6.4	5.8	1.1	0.270
Last Systolic	-0.0	0.0	-2.1	**0.038**
Last Diastolic	0.0	0.0	1.5	0.136
Last Urea	0.0	0.1	0.8	0.411
Last Urate	-0.0	0.0	-o.4	0.717
Last Haemoglobin	-0.2	0.1	-1.1	0.268
Last Hct	4.5	5.1	0.9	0.376
Last Platelet	-0.0	0.0	-0.5	0.644
Last Alk Phos	0.0	0.0	1.0	0.302
Last Ast	0.0	0.0	0.8	0.429
Last Alt	-0.0	0.0	-1.8	0.074
Last γGT	0.0	0.0	0.3	0.800
Last Albumin	-0.0	0.0	-1.8	0.076
Last Proteinuria	0.0	0.0	1.7	0.096
Delivery Gestation	0.1	0.1	1.2	0.234
Birth Weight	-0.0	0.0	-0.5	0.613
Weight Centile	0.0	0.0	0.5	0.641
Apgar 1 Minute	0.4	0.0	13.1	**0.000**

Table 6.27

These tables show the results of multiple regression analysis using the Apgar at 5 minutes as the dependent variable. This demonstrates the close **independent** relationship between the Apgar at 5 minutes and the Apgar at 1 minute and the last systolic blood pressure. There is no significant relationship with any of the other parameters. The significance of the F Ratio demonstrates that this calculation is valid.

	Presenting <30 wks	>30 wks	Total	P value
Total	57	129	186	
Alive	36	123	159	<0.0001
Normal Umbilical Artery S/D (106)	16 (33)	68 (73)	84	<0.0001
Normal Uteroplacental S/D	11 (33)	54 (73)	65	<0.0001
Reactive Cardiotocograph	29	77	106	<0.05
Decelerative Cardiotocograph	16	14	30	<0.005
Normal amniotic fluid volume (142)	30 (48)	75 (94)	105	<0.05
<10th centile birthweight	27	38	65	<0.01
Delivered for fetal reasons	32	38	70	<0.001
Delivered for maternal indications	19	43	62	NS
Thrombocytopenia ($<150x10^3$)	18	39	57	NS
Hyperuricaemia (>350 mmol/l)	49	113	162	NS
Proteinuria ≥5mg/24 hours	18	24	42	<0.05

Table 6.28

Summary of maternal and fetal monitoring in all 186 pregnancies compared with gestation at presentation. Not all the tests were available over the nine year period. Doppler Ultrasound and liquor volume estimations were available only in the latter half of the study. The relevant numbers of the tests carried out are in brackets. It is clear that there is significantly worse monitoring results in those pregnancies presenting less than 30 weeks than those presenting after that time. These tests tend to be those assessing the fetus wellbeing rather than the maternal disease.

	Alive	Demise	Total	P value
Total	38	19	57	
Normal Umbilical Artery S/D (33)	13 (23)	3 (10)	16	<0.05
Normal Uteroplacental S/D (33)	10 (23)	1 (10)	11	<0.005
Reactive Cardiotocograph	27	2	29	<0.0001
Decelerative Cardiotocograph	10	6	16	NS
Normal amniotic fluid volume (48)	23 (32)	7 (16)	30	<0.005
<10th centile birthweight	12	15	27	<0.01
Delivered for fetal reasons	16	16	32	<0.005
Delivered for maternal indications	13	6	19	NS
Thrombocytopenia (<150x10^3)	10	8	18	NS
Hyperuricaemia (>350 mmol/l)	32	17	49	NS
Proteinuria ≥5mg/24 hours	10	8	18	NS
Delivered after 30 weeks	19	2	21	<0.005

Table 6.29

A comparison of monitoring tests compared with outcome in pregnancies presenting less than 30 weeks gestation. Doppler Ultrasound and liquor volume estimations were available only in the latter half of the study. The relevant numbers of the tests carried out are in brackets. It is not surprising that there was a significant difference in tests of fetal wellbeing between those that survived and those that did not. Differences are not seen in the traditional tests of disease severity such as proteinuria, hyperuricaemia, and thrombocytopenia.

Reasons why patients were referred

Diastolic blood pressure above 90 mmHg
Proteinuria on stick testing
Past history of hypertension in pregnancy
Preexisting hypertensive problem
Known renal disease

Table 7.1

The recommendations and the reasons for referral to the Daycare Unit. These criteria were not binding on the consultant obstetrician and were not decided upon by the author.

Routine:	Five blood pressure readings at hourly intervals
	Abdominal palpation
	Serum Uric Acid (Redman, Beilin and Wilkinson, 1976)
	Haemoglobin
	Platelet Count (Redman, Bonnar and Beilin, 1978)
	Cardiotocograph
Follow-up:	Ultrasound assessment
	Estimation of fetal weight (Jeanty *et al.*, 1984)
	Liquor volume estimation
	Biophysical profile (Manning, Platt and Sipos, 1980)

Table 7.2

The monitoring tests carried out at the Daycare Unit on the day of attendance. Results are available on the same day. The follow-up assessments are carried out in those patients returning to Daycare for a second attendance or if there is a particular risk to the pregnancy.

Low risk
Average diastolic blood pressure < 90 mmHg
Uric Acid < 350 mmol/l
Platelet count > 200 x 10^9
Absence of proteinuria
Reactive cardiotocograph
Absence of IUGR

moderate risk
Average diastolic blood pressure >90 but < 100 mmHg
Uric Acid > 350 but <450 mmol/l
Platelet count < 200 but >100 x 10^9
proteinuria < ++ or < 1.5gm/24hrs
Reactive cardiotocograph
Signs of IUGR but adequate liquor volume

high risk
Average diastolic blood pressure > 100 mmHg
Uric Acid > 450 mmol/l
Platelet count < 100 x 10^9
proteinuria > ++ or > 1.5gm/24hrs
Non-reactive cardiotocograph
Signs of IUGR or reduced liquor volume

Table 7.3

Risk categories used at Daycare for the assessment of the patients. To be low risk, **all** the parameters must be met. If **any** of the parameters in the moderate or high risk category were met, that classified the patient into that group. Therefore, the patient was classified into the **highest** risk category that any of the parameters met. Those at low risk were referred back to the antenatal clinic, moderate risk patients were referred back to Daycare and the high risk patients were admitted to hospital.

Year	80	81	82	83	84	85	86	87	88	89
Deliveries	3817	3733	3585	3828	3919	4245	4301	4308	4198	4022
Total Hypertension	563	551	534	584	604	682	691	676	643	634
Daycare Referrals	0	25	75	245	423	456	485	492	482	473
Daycare Attendances	0	45	110	331	779	957	1134	1059	1102	1092
Hypertension Admissions	352	343	256	184	146	134	121	135	120	115
Inpatient Days	1065	1197	921	770	790	736	376	428	372	352
Antenatal bed Occupancy		57	55	46	34	27	24	27	22	20

Table 7.4

The effects of the opening of Daycare in August 1981 on the numbers of hypertensive patients monitored, admitted, the total number of inpatient days and the overnight antenatal bed occupancy in the years 1980-89 in The Glasgow Royal Maternity Hospital. Included in the total hypertension includes those admitted for induction of labour at term. These are **not** included as hypertension admissions. There has been a dramatic decrease in the number of patients admitted and the beds occupied.

	Referral diastolic BP	Daycare diastolic BP
Average	93±6 mmHg	83±8 mmHg
<90	278	2446
≥90 and <100	2138	624
≥100 and <110	566	86
≥110 mmHg	174	0

Table 7.5

The average blood pressure and the incidence at four levels at time of referral and at the first Daycare attendance. Blood pressure was found to be lower with the majority being less than 90 mmHg at Daycare.

		Initial Management			Long term outcome			
	Number	**Return to ANC**	**Return to DC**	**Admitted to ward**	**Admitted for Induction**	**Admitted at any time**	**Perinatal mortality**	**PNM /1000**
Low Risk	**1956**	1765	95	0	96	126	3	1.5
Medium Risk	**1105**	379	505	95	126	315	5	4.5
High Risk	**95**	0	32	33	30	65	3	31.5
Total	**3156**	**2144**	**632**	**128**	**252**	**506**	**11**	**3.5**
Admitted at any time	506	187	191	128		506	6	11.9
Perinatal Mortality	11	2	1	2	0	6		
PNM/1000	3.5	0.9	1.6	15.6	0	11.9		

Table 7.6

The initial risk assessment at Daycare, initial management, long term management compared to perinatal mortality for the patients attending Daycare from August 1981 to December 1989. The rows refer to the risk categories each patient was given at their **first** Daycare attendance. By following the rows, the columns give the initial and long term outcome for each risk group. The lower part of the table gives the overall admission rate and perinatal outcome dependent on initial and long term management. Patients admitted for induction are not included in the 'Admitted at any time' column as this only refers to those admitted for antenatal care.

Hospital	Deliveries	No of admissions	Admissions /1000 Del	No of inpatient days	Inpatient days /1000 Del
A	9077	478	53	1353	149
B	8641	446	52	2628	304
D	7200	349	48	1283	178
GRMH	8609	256	30	804	93

Table 7.7

A comparison of number of admissions and inpatient days spent due to hypertension in pregnancy in The Glasgow Royal Maternity Hospital and the three other large maternity hospitals in the West of Scotland. These hospitals did not have a Daycare unit at the time of study. Figures are the totals for the years 1986/87.

Group	Study	Number	Age	Range
A	Non-pregnant	20	22.3±3.2	18-26
B	Cross-sectional	208	21.5±4.3	16-35
C	Serial study	40	21.6±4.6	17-28

Table 8.1

Patient Groups for the cross-sectional and serial studies of normal pregnancy.

The non-pregnant controls were recruited from the nursing staff within the hospital. None had used hormonal contraceptive for the three months prior to sampling. The cross-sectional and the serial sampled patients were randomly selected from the Monday antenatal clinics at Glasgow Royal Maternity Hospital. All were normal at inclusion into the study. The pregnancy outcome was also noted and no patient developed hypertension or intrauterine growth retardation.

There was no difference between groups as regards age (Students 'T' test).

Group	Study	Number	Age	Range	Gestation
D	Prospective Primigravida	300	22.4±5.2	16-36	29.2±0.9 wks
E	PIH (Cross-sectional Study)	141	25.2±5.2	14-38	34.4±5.2 wks
F	Moderate PIH (Serial Study)	40	24.3±4.7	18-28	32.3±3.5 wks
G	Ess. hypertension (Serial Study)	34	28.2±4.9	18-35	24 wks

Table 8.2

The four patient groups studied for changes in platelet size related to pregnancy induced hypertension (PIH) and essential hypertension.

Group D were randomly selected from primigravida attending the antenatal clinics at Glasgow Royal maternity Hospital. All were between 28 and 30 weeks when sampled. The outcome of their pregnancies were noted and compared with the results of the platelet studies.

Of the 141 patients with pregnancy-induced hypertension (PIH) (Group E), 107 had moderate PIH: (diastolic blood pressure 91-109 mm mercury on two occasions, without proteinuria); and 34 had severe PIH or preeclampsia: (diastolic blood pressure greater than 110 mm mercury with proteinuria of at least 0.3 gm/24 hours) at time of sampling.

Groups F and G were recruited from patients being managed in the Daycare Unit. This allowed serial sampling of platelet size to be correlated with other manifestations of disease progression.

None of Group F were on any form of antihypertensive therapy when first selected for this study.

	Number	Platelet Count	MPV	PDW
Non-pregnant Controls	20	256.0±33.6	8.5±0.4	15.0±0.4
1st Trimester	26	254.6±41.3	8.3±0.6	15.0±0.4
2nd Trimester	87	260.8±58.9	8.4±0.9	15.0±0.4
3rd Trimester				
27-33 weeks	40	274.3±67.5	8.4±1.0	15.5±0.5
34-40 weeks	55	257.6±62.7	8.9±1.1	15.8±0.6

Table 8.3

The cross sectional study of platelet size changes in normal pregnancy. (Groups A&B) The changes seen in mean platelet volume (MPV) ($p < 0.05$) and platelet distribution width (PDW) ($p < 0.001$) are seen in the third trimester. In MPV this is only found after 34 weeks.

	Number	Platelet Count	MPV	PDW
3rd Trimester	40	255.7±76.7	8.5±1.1	15.5±0.6
Labour	40	249.3±65.7	8.8±1.2	15.8±0.5
5th day postnatal	40	329.0±75.3	7.5±0.9	15.5±0.6
6th week postpartum	20	318.0±77.7	8.5±1.0	15.1±0.5

Table 8.4

The sequential study of platelet size in the third trimester, normal labour and puerperium. There is a further rise in MPV and PDW during labour with a fall in MPV post-delivery coinciding with the rise in platelet count. Results have returned to normal by the 6th postnatal week.

Outcome	Number	%	Hct	MPV	Pl Ct
All	300	100	35.5+2.1	8.5+0.5	268+35.8
Normal	216	70	35.5+2.0	8.6+0.5	277+35.7
Mild PIH	62	21	35.6+2.1	8.7+0.9	270+58.9
Moderate PIH	13	7	35.9+3.4	8.7+1.4	270+51.0
Severe	9	3	34.5+2.8	8.8+1.5	246+79.1

Table 8.5

The outcome of the pregnancies in the 300 primigravid patients screened at 28-30 weeks. (Value + SD) There is a trend towards a lower haematocrit, larger MPV and lower platelet count in the patients who developed severe disease.

MPV	Number	Normal	Mild	Moderate	Severe
≥8.5	154	106	32	8	8
<8.5	146	110	30	5	1
Significance		NS	NS	NS	p<0.02

Table 8.6

Outcome of the pregnancies in patients with MPV above or below the normal mean for the gestation. Significantly more patients developed severe hypertension if the MPV was greater or equal to the mean value (8.5). This produces a high sensitivity for severe disease of 8/9 or 88.9%. Because the incidence of the severe disease is low, the specificity is only 145/291=49.8% and the positive predictive value is only 8/154=51.9%.

	Number	Platelet Count	MPV	PDW
Prior to 34 weeks				
Normals	40	274.3±67.5	8.4±1.0	15.5±0.5
Moderate PIH	35	277.5±49.5	8.5±1.3	15.4±0.4
Severe PIH	14	148.8±24.0	8.7±0.3	15.4±0.5
At or after 34 weeks				
Normal	55	257.6±62.7	8.9±1.1	15.8±0.6
Moderate PIH	72	271.3±79.1	9.0±1.4	15.8±0.6
Severe PIH	20	212.3±51.0	11.2±1.3	15.9±0.7

Table 8.7

Platelet changes in patients with moderate or severe PIH. If the disease presents prior to 34 weeks, the platelet count is reduced with no change in MPV. A smaller reduction in count is seen with a large change in MPV after 34 weeks. The PDW did not change, implying that the whole population of platelets changed volume, not just a subpopulation.

Outcome	Number	24 wks	28wks	32wks	36wks
Stable	20	8.5+1.2	8.6+1.0	8.8+1.4	8.7+1.1
Moderate	8	8.7+1.0	8.7+1.1	8.9+1.3	9.1+1.3
Severe	6	8.6+1.2	9.1+1.4	9.7+1.2	10.2'1.2
Significance		NS	NS	$p<0.01$	$p<0.005$

Table 8.8

Outcome of the 34 patients with essential hypertension sampled serially and the changes in the mean platelet volume (MPV). The total numbers for each group reduce as gestation increases as patients are delivered. The significant differences were found between the severe group and those patients that remained stable.

Outcome	Number	At diag	1 wk	2wk	3wks
Stable	17	8.6+1.1	8.8+1.2	8.9+1.3	9.0+1.1
Moderate	14	8.8+1.2	9.0+1.2	9.1+1.4	9.2+1.2
Severe	9	8.8+1.3	9.1+1.4	10.0+1.2	11.2±1.2
Significance		NS	NS	$p<0.005$	$p<0.001$

Table 8.9

Outcome of the 40 patients with mild pregnancy induced hypertension sampled serially and the changes in the mean platelet volume (MPV). The timings are related to the time the diagnosis was made and the weeks after the diagnosis was made not to gestation. The total numbers for each group reduce as the weeks increase. The significant differences were found between the severe group and those patients that remained stable.

	Normal 3rd Trimester Pregnancy	Mild/Moderate PIH	Severe PIH
Number	40	26	15
Primigravid	23 (57.5%)	18 (69%)	10 (66.6%)
Parous	17 (42.5%)	8 (31%)	5 (33.3%)
Mean Age (years±SD)	25.2±5.8	26.1±5.7	25.3±5.4
Mean±SD Gestation at time of first sample (wks)	35.2 + 4.0	33.9 + 5.1	29.7 + 2.9
Number with significant proteinuria (>0.3 gm/24 h)	0	3 (11%)	10 (66.6%)
Number with IUGR*	0	3 (11%)	10 (66.6%)
Live Births	40 (100%)	26 (100%)	15 (100%)

* **IUGR** = Intra Uterine Growth Retardation = Birth Weight < 10th centile.

Table 9.1

Patient characteristics of those involved in the cross-sectional study of PGI_2M and TxB_2 in normal and hypertensive pregnancy. The severe patients not only had a nigher incidence of IUGR but also presented earlier. There was no perinatal mortality.

	Non pregnant	1st Trimester	2nd Trimester	3rd Trimester	Postnatal
PG12M	15.9±0.68	19.9±0.96***	15.5±1.05¶	16.4±1.2¶	13.6±1.99¶
TxB2	142±4.9	131±14.2*	133±14.9*	123±10.7**	119±6.3***
Number	44	29	31	29	21

*** p<0.01, ** p<0.02, * p<0.05 compared with non-pregnant.
** p<0.01, ¶ p<0.05, compared with 1st Trimester.

Table 9.2

Plasma levels of prostacyclin metabolites (PG12M) and Thromboxane B_2 (TxB_2) in non-pregnant women, the three trimesters of pregnancy and the puerperium. Results are mean±SEM.

	1st Trimester	2nd Trimester	3rd (1) Trimester	(2)
Normal	19.1±2.5	13.1±1.2*	13.3±1.8*	
PIH	17.6±2.5	18.2±2.1	12.2±3.4	<5.0*+

* $p < 0.05$ compared with 1st trimester of same group
+ $p < 0.05$ compared with 2nd trimester of same group.

(1) = 32-36 weeks gestation **(2)** = 37-40 weeks gestation

Table 9.3

The serial changes in the PGI_2M in those who remained normotensive and those who developed PIH in the third trimester. The PIH group had higher levels in the 2nd trimester although this did not reach significance.

	1st Trimester	2nd Trimester	3rd (1) Trimester	(2)
Normal	125.0±8.8	94.8±13.8*	75.3±5.0**	
PIH	131.5±12.6	82.2±12.6*	74.0±5.0*	113.6±10.4+

* $p < 0.05$ compared with 1st trimester of same group
** $p < 0.02$ compared with 1st trimester of same group
+ $p < 0.05$ compared with 3rd trimester of same group.

(1) = 32-36 weeks gestation **(2)** = 37-40 weeks gestation

Table 9.4

The serial changes in the TxB2 in those who remained normotensive and those who developed PIH in the third trimester. The PIH group had higher levels towards the end of pregnancy but this did not reach significance.

	Hydrallazine	Labetalol	Nicardipine
Number	15	15	20
Age	23.4±3.4	24.2±4.1	22.9±4.6
Gestation	31.3±3.5	32.1±3.9	31.9±4.1
Systolic BP	155.32±15.3	154.26±14.7	156.21±15.8
Diastolic BP	106.43±8.5	105.67±7.6	106.21±8.1

Table 10.1.

The patient groups in the acute hypertension study. The hydrallazine and labetalol groups were randomised separately. The nicardipine study was done at a later time. There was no difference in the parameters between any of the groups. Although the criteria for entry was a diastolic blood pressure of above 105 mmHg, some patients had a blood pressure below this at commencement of the study. No patient had a diastolic blood pressure below 100 mmHg.

(Values are given as means±SD)

	Labetalol		Hydrallazine		Nicardipine
Number	**15**		**15**		**20**
Self Assessment					
Felt better	**5**		**4**		**6**
No change	**9**		**5**		**6**
Felt worse	**1**	**<- p<0.05 ->**	**6**		**3**
Side Effects					
Headache	**0**		**4**		**2**
Nausea	**0**		**2**		**0**
Peripheral Tremor	**2**		**2**		**0**
Scalp Tingling	**3**		**0**		**0**
Total with side effects	**3**		**6**	**<- p<0.05 ->**	**2**

Figure 10.2

The patients subjective assessment of the therapy given and the side effects reported when questioned for each of the study drugs. More patients felt either no better or worse after hydrallazine than with the other two drugs ($p<0.05$ for difference between labetalol and hydrallazine). This was usually due to experiencing headache. The incidence of side effects was significantly higher with hydrallazine as compared to nicardipine ($p<0.05$)

	Labetalol Group	Control group
Primigravida	38	36
parous	26	26
Total	**64**	**62**
Age	23.8 ± 3.4	24.1 ± 2.9
Gestation	34.86 ± 2.23	35.22 ± 2.14
Systolic BP	142.59 ± 10.02	139.78 ± 9.13
Diastolic BP	97.46 ± 7.6	95.02 ± 5.29
Rise in Sys BP	14.78 ± 9.02	11.71 ± 8.26
Rise in Dias BP	19.26 ± 13.33	16.16 ± 12.58
Plasma Urate	308.09 ± 84.0	306.00 ± 72.02
Platelet Count	220.13 ± 50.0	239.41 ± 74.20

Table 10.3

The entry parameters of the randomised study of labetalol against bed rest in mild to moderate Pregnancy Induced Hypertension. The rise in blood pressure was from the first trimester levels to the entry blood pressure.

	Labetalol Group	Control Group	Significance
Number Settled	33	9	p<0.0001
Number Stable	26	20	NS
Number worsened	5	33	p<0.001
Total	64	62	
Number severe	3	13	p<0.005
Number Proteinuria	4	9	NS
Uric acid rise	32	31	NS
Platelet Count Fall	5	25	p<0.0001

Table 10.4

A comparison of the change in the parameters between the treated and the control groups.

Settled = Diastolic blood pressure fell below 90 mmHg

Stable = Diastolic blood pressure did not rise by more than 5 mmHg.

Worsened = Diastolic blood pressure rose by more than 5 mmHg.

Severe = Diastolic blood pressure rose above 110 mmHg.

Proteinuria = Greater than 0.3 gm/24 hours.

Uric acid rise = A rise of more than 15 mmol/l (approx. 5%)

Platelet Count Fall = A fall of more than 25 x 10^3 (approx 10%)

Side Effect	Number	Withdrawals
Nasal Stuffiness	**7**	**0**
Slight Nausea	**10**	**0**
Peripheral Tremor	**21**	**2**
Scalp Tingling	**18**	**0**
Bronchospasm	**1**	**1**

Table 10.5

The side effects seen in the study group. The most common were peripheral tremor and scalp tingling. These were rarely bad enough to cause withdrawal from the study.

	Labetalol Group	Control Group	Significance
Delivery Gestation	38.78±1.35	38±12	NS
Labour			
Spontaneous	15	12	NS
Induced	40	38	NS
Elective Section	9	12	NS
Delivery			
SVD	29	28	NS
Forceps	18	15	NS
Caesarean Section	17	19	NS
Birth Weight (Kg)	3.21±0.86	3.26±0.63	NS
Number < 10th Centile	12	11	NS
Placental weight	0.62±0.15	0.60±0.14	NS
Apgar <5 at 1 min.	6	5	NS
Apgar <7 at 5 min.	3	3	NS
Perinatal Death	0	0	NS

Table 10.6

The outcome of the pregnancies as assessed by gestation at delivery, onset of labour, delivery and neonatal wellbeing in the controlled trial of labetalol against bed rest.

Parameter	Mean	Range
Number	186	
Age	24.21±4.6	18-36
Gestation	31.42±3.2	24-34
Systolic BP	154.48±16.1	135-200
Diastolic BP	109.20±9.2	100-140
Systolic Rise	25.55±9.2	10-40
Diastolic Rise	27.93±10.2	10-60
Proteinuria	2.4±1.3	0.5-6.2
Urate	387.21±82.1	260-620
Platelet Count	174.90±66.4	32-265

Table 10.7

The patient group in the severe study. Blood pressure levels as well as the rise in blood pressure form the first trimester reading are markedly elevated. The elevation of urate, the low platelet count and the degree of proteinuria confirm that these patients have significant disease.

Parameter	Mean	Range
Labetalol dose	1201±320	600-1600
Treatment length	15.6±9.2	1-36
Delivery gestation	33.5±3.1	28-38

Table 10.8

The average dose of labetalol given. 58 of these patients also received a vasodilator drug which was initially hydrallazine but latterly nifedipine. There was a wide range in treatment length, partly related to the desire to prolong the pregnancy for longer in the earlier gestations.

Parameter	Start	Week 1	Week 2
Systolic BP	154.48±16.1	135.38±7.4	135.84±10.1
Diastolic BP	109.20±9.2	93.40±6.2	91.68±8.3
Proteinuria	2.4±1.3	2.0±2.1	3.2±2.4
Urate	387.6±82.1	402.4±92.1	394.6±88.1
Creatinine Cl	109.4±23.1	106.7±25.2	94.8±35.6
Platelets	174.9±66.4	206.7±43.2	226.4±36.3

Table 10.9

The results of the treatment and the monitoring in the severe study. These results confirm the apparent platelet protective effect of labetalol therapy.

Time (min)	Pre	15	30	45	60
Systolic BP	155.5±8.7	156.6±14.6	144.9±13.2	145.4±15.2	146.6±10.6
Diastolic BP	108.0±4.3	96.6±5.6	94.9±7.8**	93.9±5.8**	93.7±4.5**
Brachial SD	3.2±1.1		3.6±1.6		3.7±2.1
Uteroplacental SD	1.6±0.5		1.8±0.8*		1.8±0.3
Umbilical SD	2.5±0.9		2.4±0.7		2.4±0.8

SD = Doppler systolic/diastolic ratio BP = blood pressure

* $p<0.05$ ** $p<0.001$ (Significance by Wilcoxon rank test for matched pairs.)

Table 10.10

Maternal blood pressure and brachial artery, uteroplacental and umbilical artery systolic/diastolic ratios pre and post nicardipine therapy (results are mean ± 1 standard deviation).

Time	Pre	1st Day	3rd Day	5th Day	7th Day	9th Day
Systolic BP	151.7±8.4	145.9±10.4	152.8±16.1	148.7±15.1	145.6±5.3	144.7±4.1
Diastolic BP	105.4±4.1	95.6±7.5*	102.1±11.8	97.9±12	99.4 ±10.3	93.2±5.3
Brachial SD	4.0±1.3	3.9±1.3	3.8±1.4	3.9±2.3	4.6±2.0	5.1±1.8
Uteroplacental SD	1.8±0.4	1.9±0.3	2.0±0.4*	1.9±0.4	1.5±0.5	1.5±0.6
Umbilical SD	2.6±0.9	2.7±0.7	2.7±0.8	2.8±0.8	2.4±0.4	2.7±1.0

SD = Doppler systolic/diastolic ratio BP = blood pressure

*$p<0.05$ (Significance by Wilcoxon Rank test for matched pairs)

Table 10.11

Maternal blood pressure and brachial artery, uteroplacental and umbilical artery systolic/diastolic ratios pre and post pindolol therapy (results are mean±1 standard deviation).

Time	Pre	1st Day	3rd Day	5th Day	7th Day	9th Day
Systolic BP	138.5±8.5	135±9.2	136.3±8.6	138.1±8.3	140.8±8.4	145.8±10.2
Diastolic BP	92.9±3.9	93.2±5.8	91.5±6.6	95.2±5.8	96.4±6.4	99.5±6.2
Brachial SD	3.3±0.6	3.8±1.4	3.4±0.8	3.5±1.2	4.0±1.8	3.8±1.7
Uteroplacental SD	1.9±0.4	2.0±0.5	2.1±0.4	2.3±0.3*	2.2±0.7	2.3±0.4
Umbilical SD	2.4±0.3	2.4±0.2	2.4±0.3	2.4±0.4	2.7±0.6*	2.5±0.5

SD = Doppler systolic/diastolic ratio BP = blood pressure

*$p<0.05$ (Significance by Wilcoxon Rank test for matched pairs)

Table 10.12

The changes in maternal blood pressure and brachial artery, uteroplacental and umbilical artery systolic/diastolic ratios in preeclamptic patients on no therapy (results are mean $\pm$ 1 standard deviation).

Prepregnancy

If patient is normotensive consider stopping all anti hypertensive drugs.

Aim to stop ACE inhibitors and diuretics if at all possible.

Less than 20 weeks

If the patient is normotensive stop antihypertensive medication and put into monitoring programme.

If presenting for the first time with hypertension, investigate for renal disease, then insert into monitoring programme.

Refer to the Outpatient Daycare Assessment unit for followup.

After 20 weeks.

Any patient that presents for the first time or with worsening BP after 20 weeks is presumed to have preeclampsia until monitoring suggests otherwise.

Monitoring

Mother:- Average of five blood pressure readings.
Serum uric acid
Platelet count
Urinalysis for protein
Optional:- plasma creatinine
24 hour urine for protein

Fetus:- Non stress test (cardiotocograph)
Ultrasound for weight and liquor volume.
Optional:- Doppler ultrasound
Biophysical profile

Criteria for antihypertensive usage

If BP is persistently elevated above 150/100 mmHg.
start Labetalol 200 mg three times a day
If BP not controlled increase to 200 mg four times a day
then increasing dosage up to 1200 mg a day
If BP not controlled add in nifedipine 10 mg twice a day
then increasing up to 40 mg a day.

Hypertensive crisis

If BP greater than 160/110 mmHg give 200 mg oral labetalol
or 50 mg IV labetalol
or 20 mg IV Hydrallazine
Repeated oral doses or an infusion of labetalol can then be used

Table 10.13

Management protocol for the use of antihypertensive drugs in the Glasgow Royal Maternity Hospital.

Glasgow Royal Maternity Hospital
Hypertensive patients

Year	Total Deliveries	Total No.	Treated No.	Treated %	Eclamptic No.	Perinatal Mortality Hyp	All	All / 1000	Hyp / 1000 hyp	Hyp/ 1000	% of all	Scottish Figures All/ 1000	Hyp/ 1000	% of all
1980	3817	432	10	2.31	2	6	62	16.24	13.89	1.6	9.68	13.1	1.2	9.16
1981	3733	423	32	7.57	1	5	55	14.73	11.82	1.3	9.09	11	0.9	8.18
1982	3585	424	45	10.61	0	7	47	13.11	16.51	2.0	14.89	11.5	0.8	6.96
1983	3828	443	63	14.22	0	1	28	7.31	2.26	0.3	3.57	10.6	0.5	4.72
1984	3919	426	76	17.84	2	3	50	12.76	7.04	0.8	6.00	11	0.7	6.36
1985	4245	436	89	20.41	1	2	43	10.13	4.59	0.5	4.65	9.8	0.7	7.14
1986	4301	472	86	18.22	2	3	54	12.56	6.36	0.7	5.56	10.2	0.6	5.88
1987	4308	403	80	19.85	1	1	44	10.21	2.48	0.2	2.27	8.9	0.3	3.37
1988	4198	426	87	20.42	0	2	49	11.67	4.69	0.5	4.08	8.9	0.4	4.49
1989	4022	432	91	21.06	0	1	33	8.20	2.31	0.3	3.03	8.1	0.2	2.47
Total	**39956**	**4317**	**659**	**15.27**	**9**	**31**	**465**	**11.69**	**7.2**	**0.8**	**6.67**	**10.31**	**0.63**	**5.87**

Table 10.14

A table showing the absolute numbers of deliveries, total numbers of patients with persistent hypertension(diastolic blood pressure above 90 mmHg) from all causes, Numbers and percentage of hypertensive patients treated with antihypertensive drugs, and the number of hypertensive patients becoming eclamptic. Also shown is the absolute number of perinatal deaths(PND) associated with hypertension, number of PND from all causes, PND rate per 1000 deliveries, PND associated with hypertension per 1000 hypertensive deliveries, PND associated with hypertension per 1000 all deliveries, and the percentage of all PND associated with hypertension. This can be compared with the Similar figures from the whole of Scotland, the overall PND rate per 1000 deliveries, PND associated with hypertension per 1000 of all deliveries and the percentage of the PND associated with hypertension.

The Illustrations or Figures

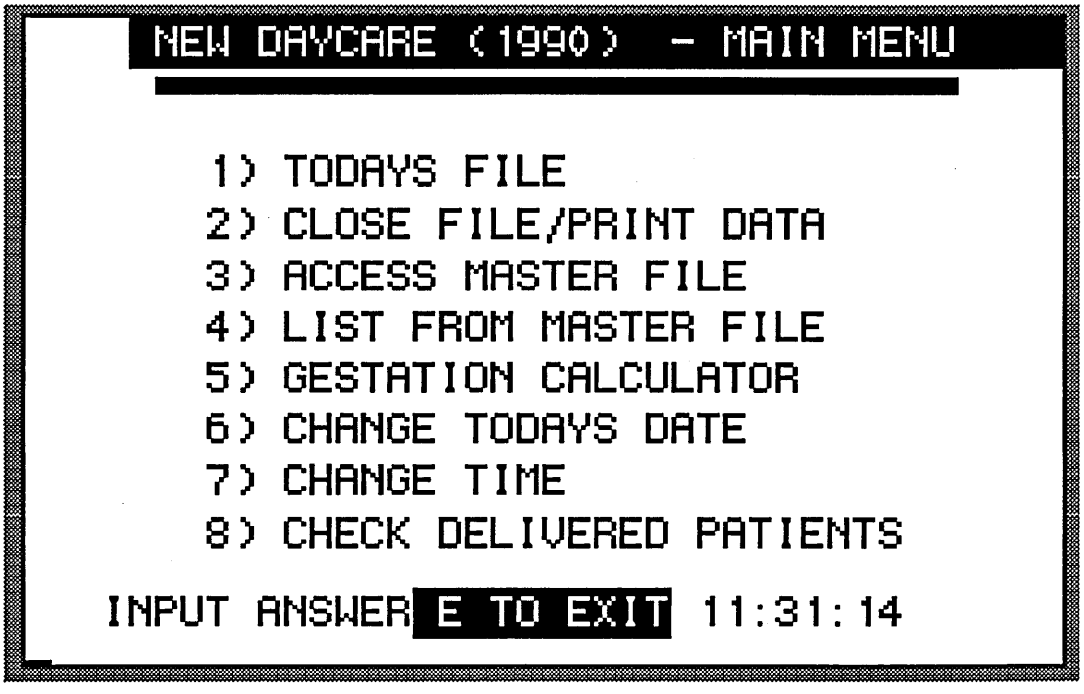


Figure 2.1

A "screendump" of the menu for the Daycare programme. It was completely menu driven and easy to use. All Daycare data from August 1984 was entered in 'real' time.

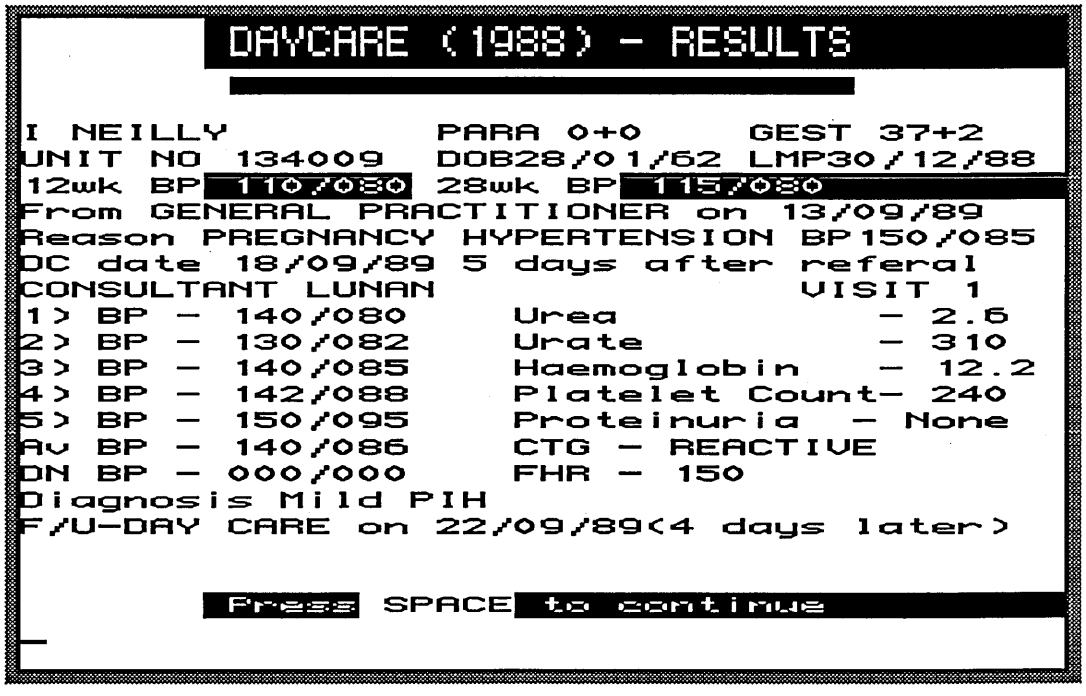


Figure 2.2

A "screendump" of the Daycare data screen displaying the available data. This is a false name and number, but the data is genuine. This patient had a single BP greater than 95 mmHg diastolic at the outpatient clinic. Therefore, she is, by definition, mildly preeclamptic. She is being seen again at Daycare to see if her blood pressure problems are progressive. This will be explained fully in Chapter 7.

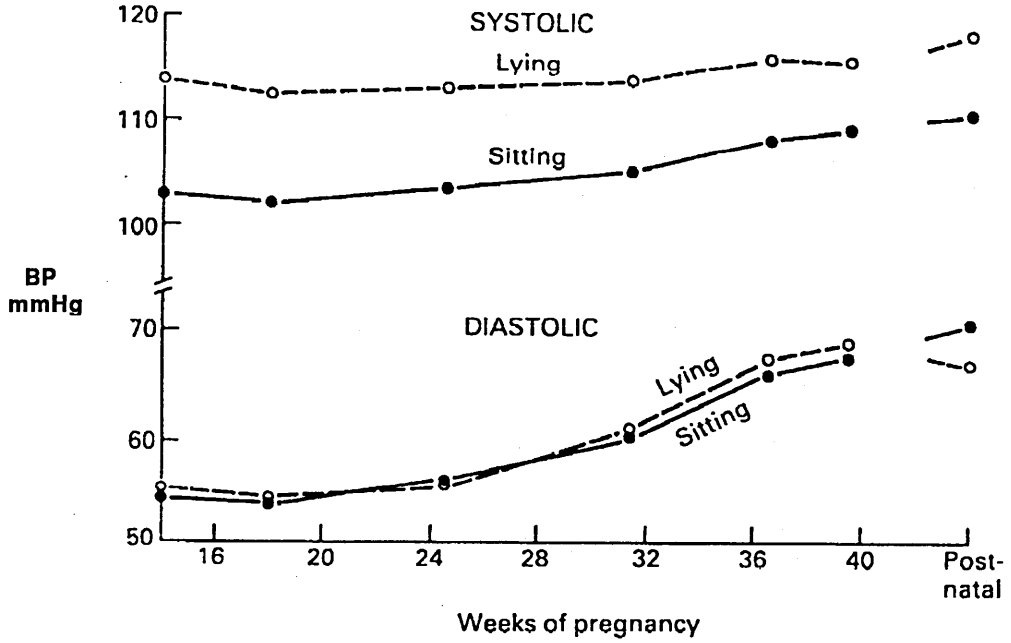


Figure 3.1

The blood pressure changes throughout normal pregnancy taken from MacGillivray (MacGillivray, 1961). There is little difference between lying and sitting as far as diastolic blood pressure is concerned, but a marked difference in systolic blood pressure.

There is a fall into the second trimester and and then a rise towards term. The blood pressure at term is little different from the non-pregnant blood pressure.

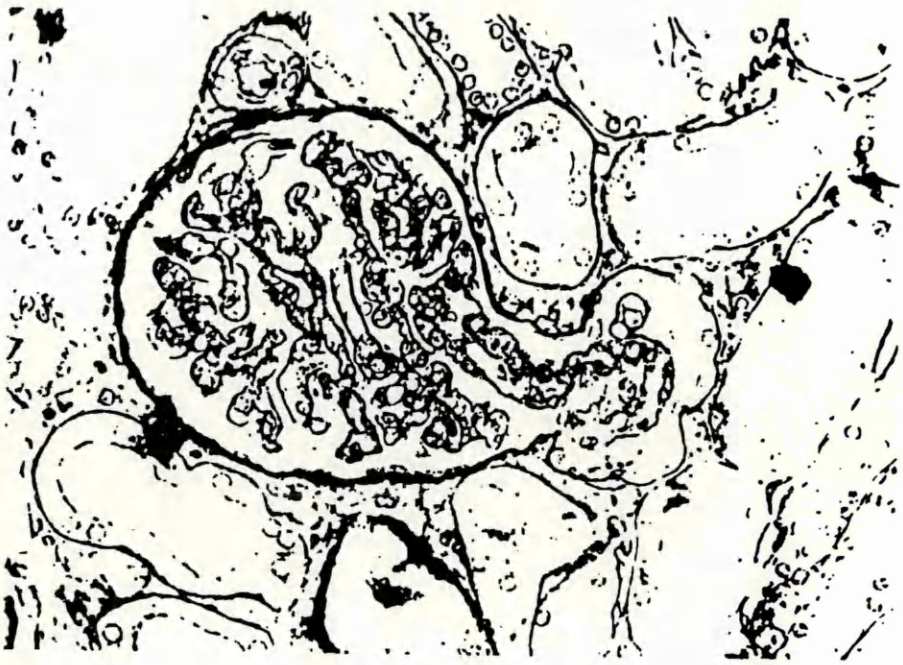


Figure 3.2

The classic renal lesion of preeclampsia. The glomerulus shows pouting of the glomerular loop into the neck and the first coil of the proximal tubule (Sheehan and Lynch, 1973).

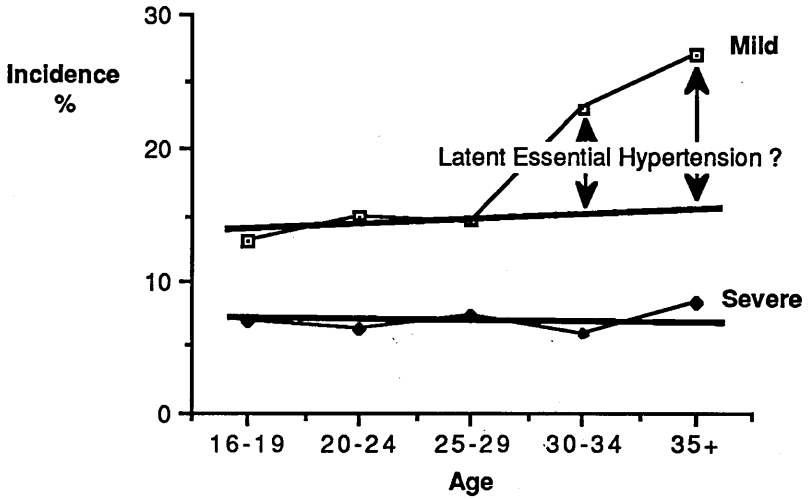


Figure 3.3

The incidence of moderate and severe preeclampsia changes with age. There is an increase of moderate hypertension with increasing age. This is probably related to the background incidence of essential hypertension (Nelson, 1955).

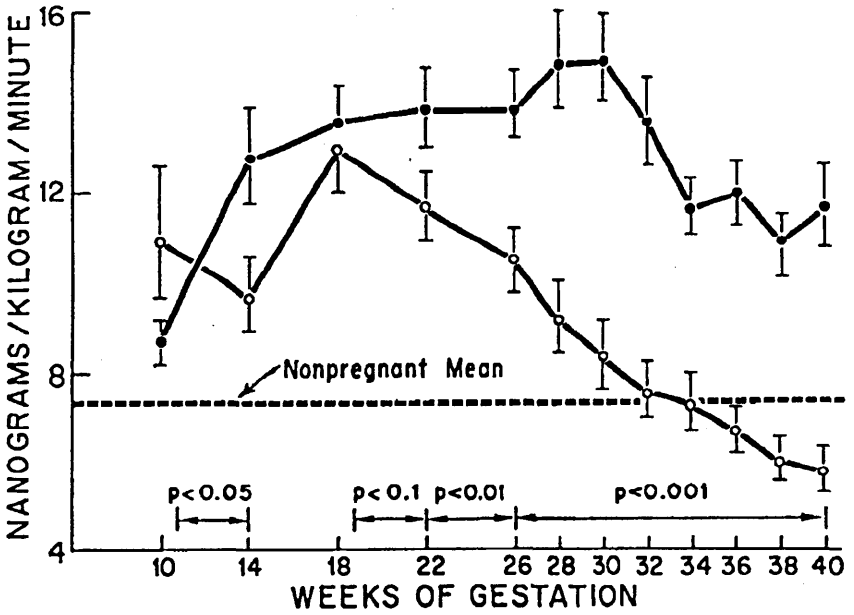


Figure 3.4

A comparison of the dose of angiotensin II required to produce a pressor response in 120 primigravida who remained normotensive (black circles) and 72 who became hypertensive in later pregnancy (open circles). There was a significant difference seen from 22 weeks, where those that developed hypertension appeared to be more sensitive (Gant *et al.*, 1973).

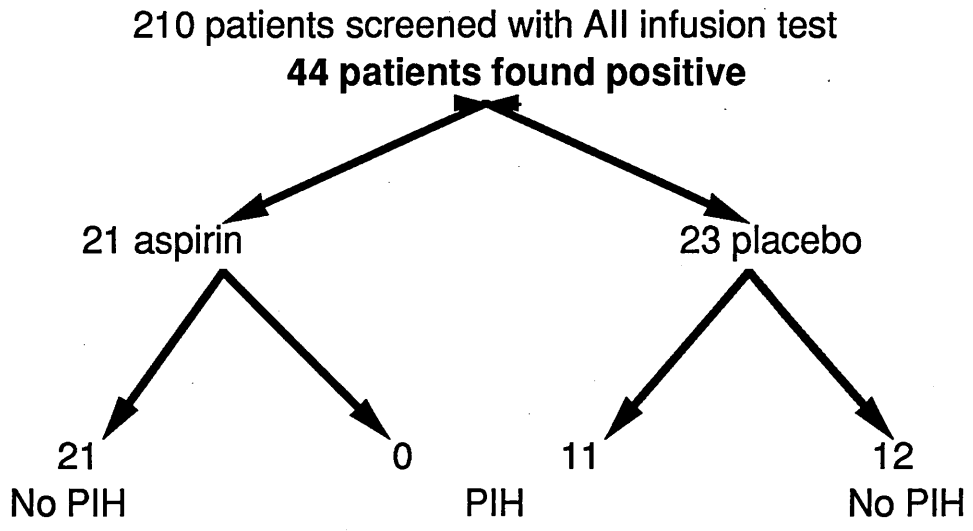


Figure 3.5

The results from a randomised study of aspirin in 44 primigravida who were found to be sensitive to angiotensin II infusion. It shows that aspirin appears to prevent the development of preeclampsia but also that only 50% of the untreated patients developed the disease (Wallenburg *et al.*, 1986).

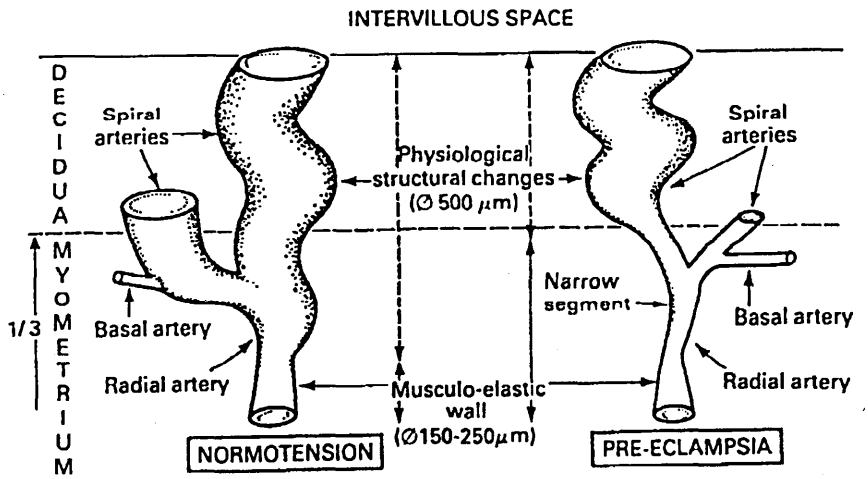


Figure 3.6

An artist's impression of the spiral arteries of the uterus in normal and preeclamptic pregnancy. Normally there is a dilatation of the artery from trophoblastic invasion destroying the muscle coat. In preeclampsia, this dilatation does not occur. This will lead to reduced placental perfusion and may explain the increase incidence of growth retardation found in preeclampsia (Robertson, Brosens and Dixon, 1976).

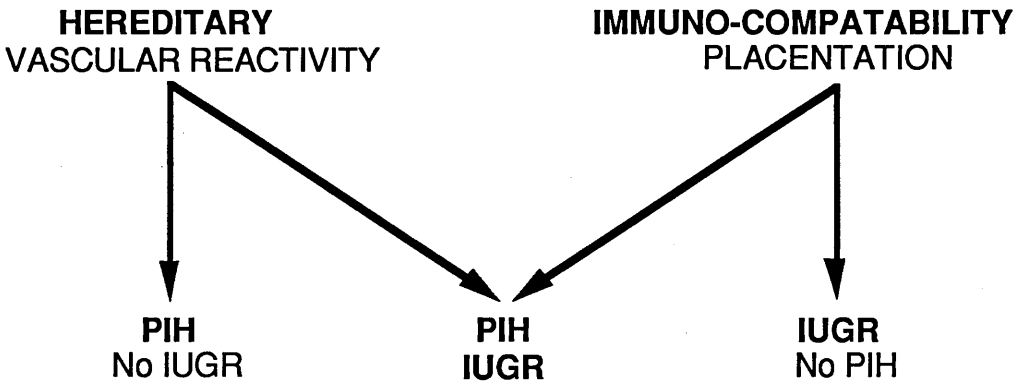


Figure 3.7

A suggested relationship between pregnancy induced hypertension and intrauterine growth retardation. If the placental lesion is present, IUGR will be apparent but there will be no blood pressure problems unless there is a vascular sensitivity. The reverse would also be true.

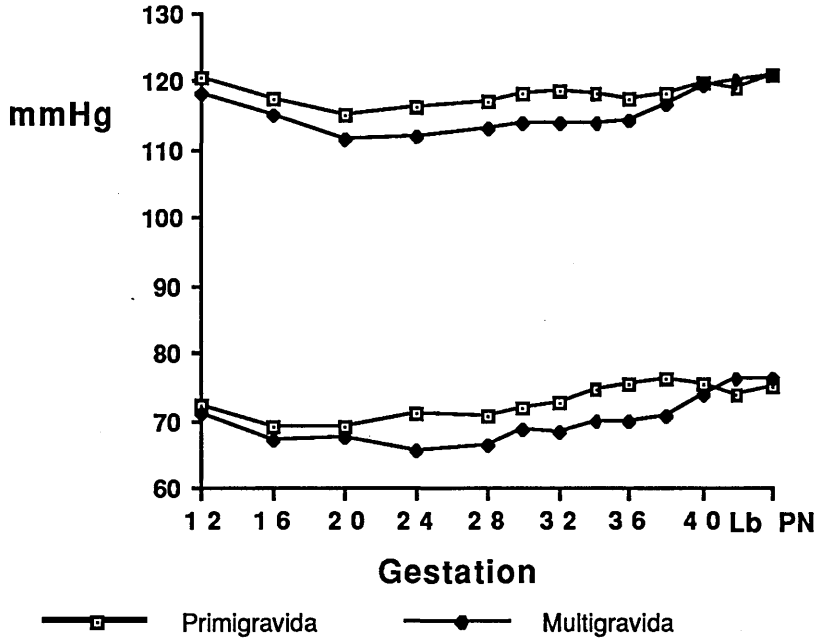


Figure 5.1

The serial blood pressure measurements in 186 primigravida and 115 multiparous randomly selected patients attending the antenatal clinic at the Glasgow Royal Maternity Hospital. The graph demonstrates a fall in blood pressure in the second trimester with a rise towards term. It was found that the parous women had a significantly lower systolic and diastolic blood pressure in mid-pregnancy (Significance shown in Table 5.2).

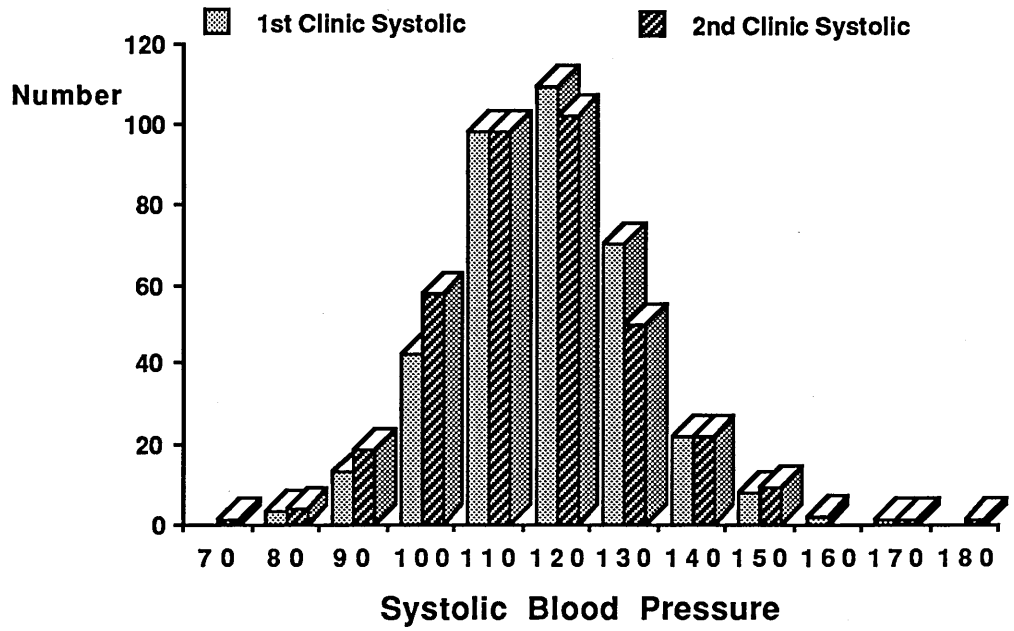


Figure 5.2

A graph of the two systolic blood pressure measurements taken in 365 randomly selected patients at the antenatal clinic by the same observer using a random zero sphygmomanometer. There was a normal distribution and no difference between the mean or range of the two readings.

Each column corresponds to the number of patients with a reading between the given figure and 9 mmHg above, e.g. the first column is the number of all readings between 70-79 mmHg.

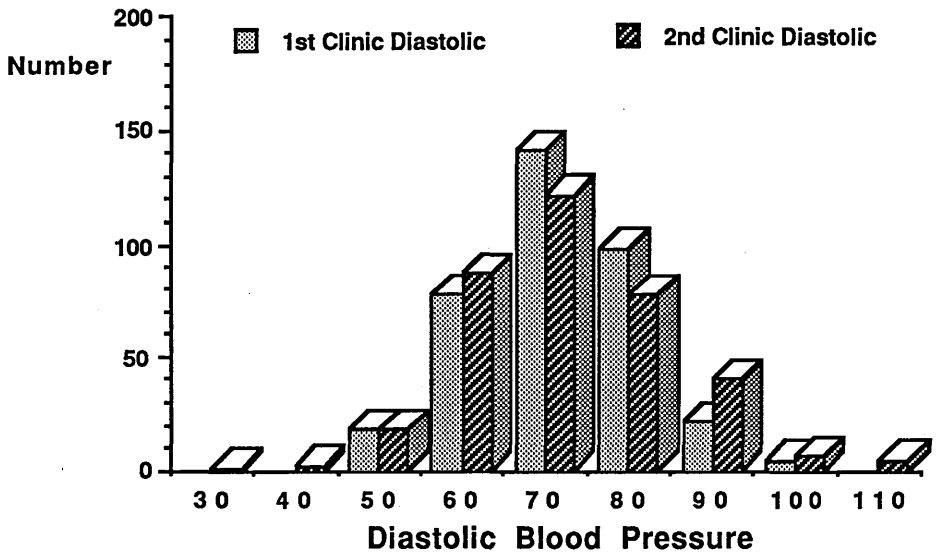


Figure 5.3

A graph of the two diastolic blood pressure measurements in 365 randomly selected patients taken at the antenatal clinic by the same observer using a random zero sphygmomanometer. There was a normal distribution and no difference between the mean or range of the two readings.

Each column corresponds to the number of patients with a reading between the given figure and 9 mmHg above, e.g. the first column is the number of all readings between 30-39 mmHg.

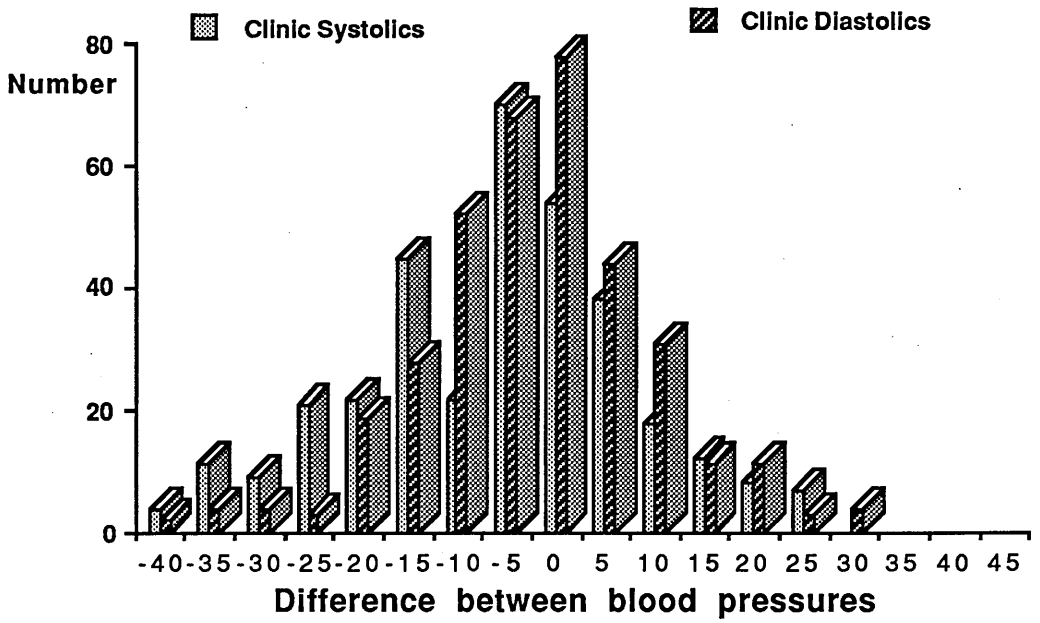


Figure 5.4

A graph showing the difference between two consecutive readings taken 10 minutes apart in 365 randomly selected patients at the antenatal clinic by the same observer using a random zero sphygmomanometer. There was a wide disparity between the consecutive readings and less than 40% of the patients had readings within 5 mmHg. The difference could either be up or down.

Each column corresponds to the number of patients with a difference between the given figure and 4 mmHg above, e.g. the first column is the number of patients where the second reading is between 36-40 mmHg less than the first reading.

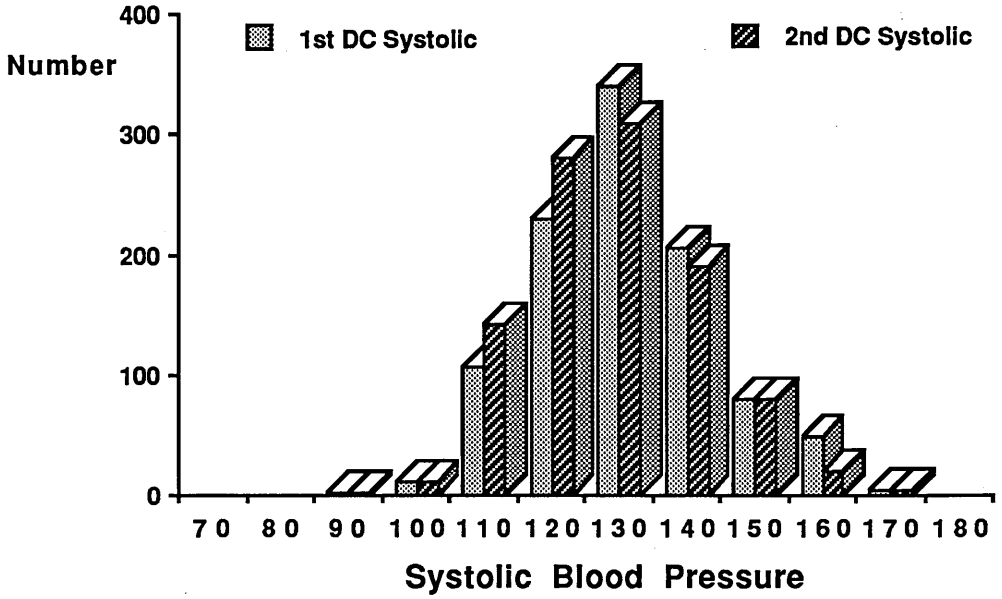


Figure 5.5

A graph of the first two systolic blood pressure measurements taken in 1000 consecutive Daycare patients by the attendant nursing staff using a mercury sphygmomanometer. There was a normal distribution and no difference between range of the two readings. There was a small but highly significant difference in the means. (131.2±12.9 mmHg v 128.7±12.8 mmHg, $p<0.001$ (Student's T Test))

Each column corresponds to the number of patients with a reading between the given figure and 9 mmHg above, e.g. the first column is the number of all readings between 70-79 mmHg.

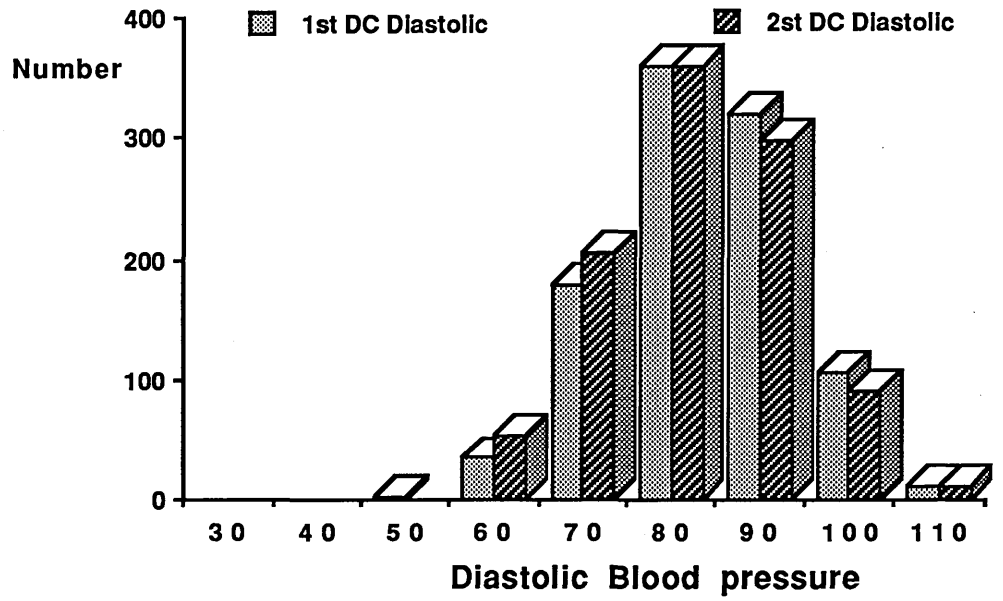


Figure 5.6

A graph of the first two diastolic blood pressure measurements taken in 1000 consecutive Daycare patients by the attendant nursing staff using a mercury sphygmomanometer. There was a normal distribution and no difference between range of the two readings. There was a small but significant difference in the means. (84.8±10.8 mmHg v 83.5±10.3 mmHg, $p<0.005$, (Student's T Test))

Each column corresponds to the number of patients with a reading between the given figure and 9 mmHg above, e.g. the first column is the number of all readings between 30-39 mmHg.

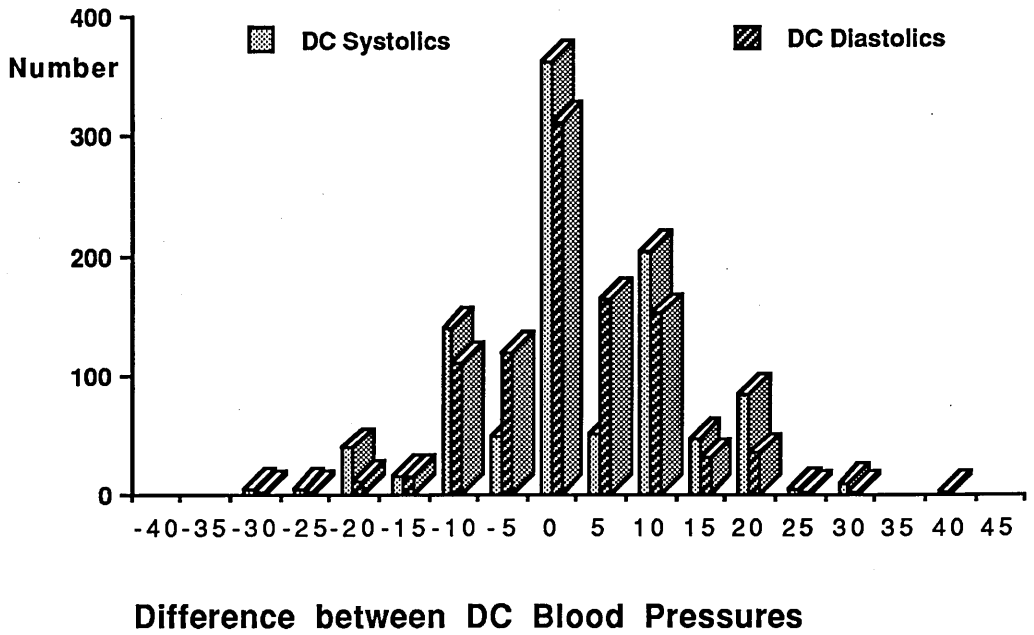


Figure 5.7

A graph showing the differences between the first blood pressures readings taken in 1000 consecutive Daycare patients by the attendant nursing staff using a mercury sphygmomanometer. There was a wide variation in the consecutive readings and in less than 50% of the patients was the second blood pressure within 5 mmHg of the first. The difference could either be up or down.

Each column corresponds to the number of patients with a difference between the given figure and 4 mmHg above, e.g. the first column is the number of patients where the second reading is between 36-40 mmHg less than the first reading.

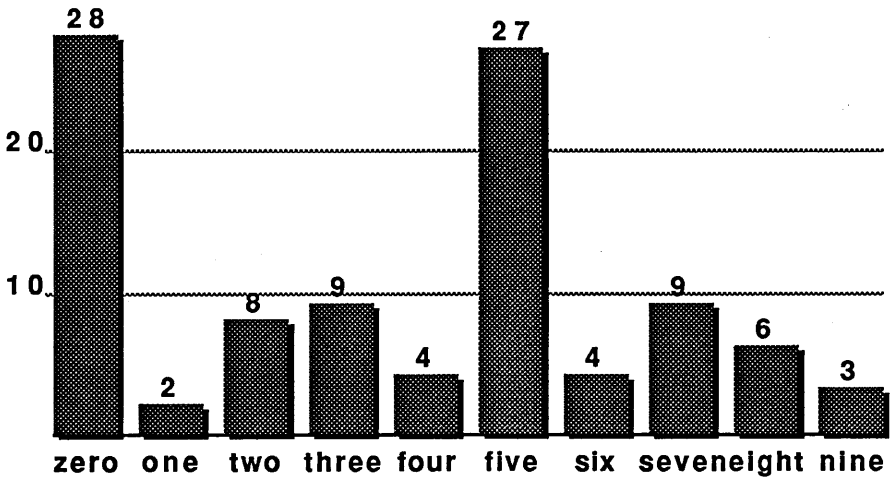


Figure 5.8

The incidence in percent of Diastolic blood pressure readings ending in the quoted digits in the combined group of the first and second Daycare readings by the attendant midwives. There appears to be a predominance of readings ending in zero and five and a reluctance to give a reading ending in 1,4,6 or 9 mmHg.

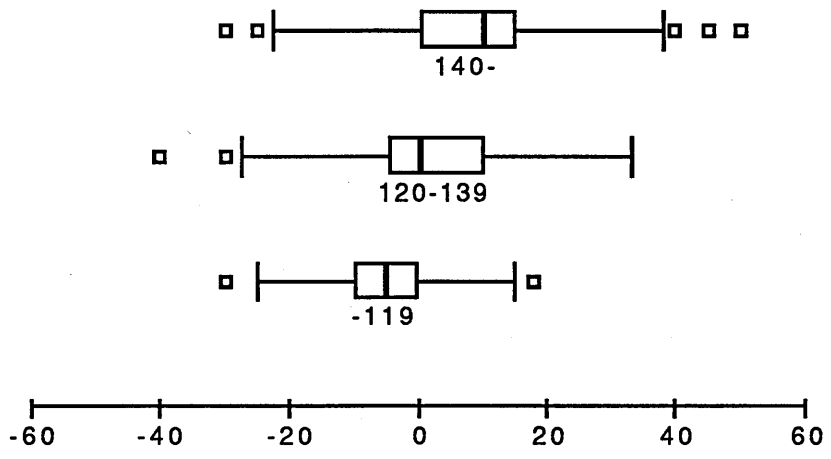


Figure 5.9

A "Box and Whiskers" graph of the changes in systolic blood pressure taken in 1000 consecutive Daycare patients by the attendant nursing staff using a mercury sphygmomanometer. The data represents the differences separated depending on the first systolic blood pressure.

The results demonstrate that for the higher blood pressures there is a tendency for the blood pressure to fall (a positive difference) and to rise with the lower blood pressures. These differences are all highly significant ($p<0.001$) although there is an obvious overlap.

The graph shows the median (horizontal line), confidence limits of the mean (the Box), SDx3 (the whiskers) and the outliers (the small boxes)

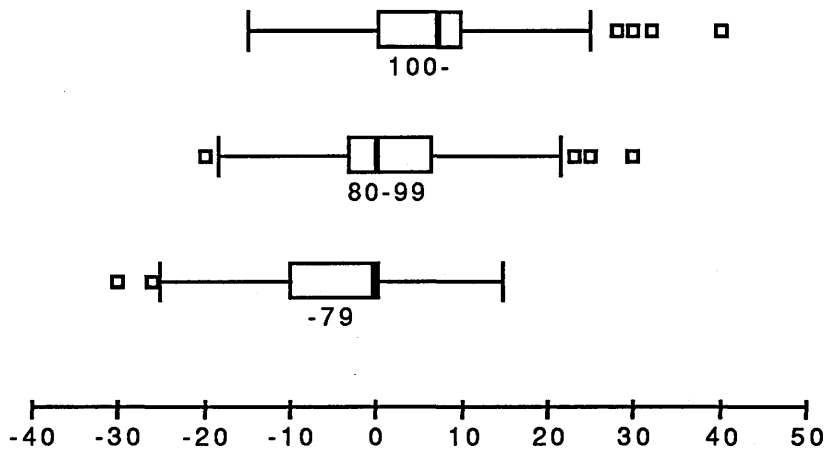


Figure 5.10

A "Box and Whiskers" graph of the changes in diastolic blood pressure taken in 1000 consecutive Daycare patients by the attendant nursing staff using a mercury sphygmomanometer. The data represents the differences separated depending on the first diastolic blood pressure.

The results demonstrate that for the higher blood pressures there is a tendency for the blood pressure to fall (a positive difference) and to rise with the lower blood pressures. These differences are all highly significant ($p<0.001$) although there is an obvious overlap.

The graph shows the median (horizontal line), confidence limits of the mean (the Box), SDx3 (the whiskers) and the outliers (the small boxes)

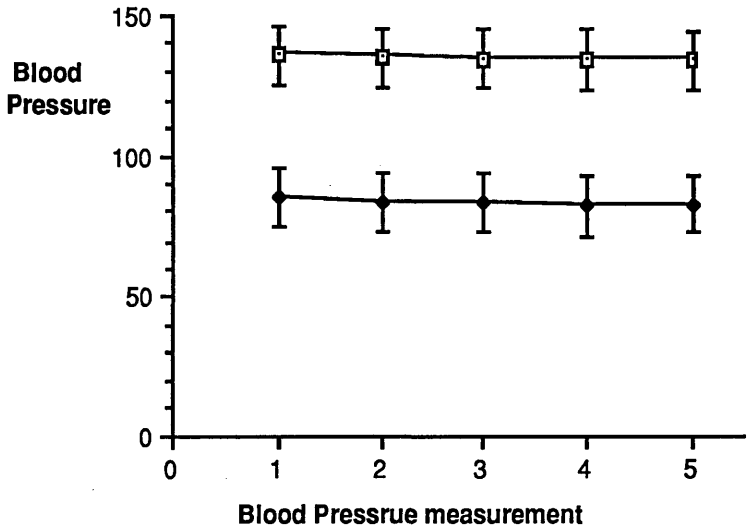


Figure 5.11

The trend of the five diastolic blood pressure readings at Daycare. There was a small but significant difference between the means of the first and second readings. These differences were only 2.5 mmHg for the systolic blood pressure and 1.3 mmHg for the diastolic blood pressure. There was no difference between the later readings (Readings are in mmHg±SD).

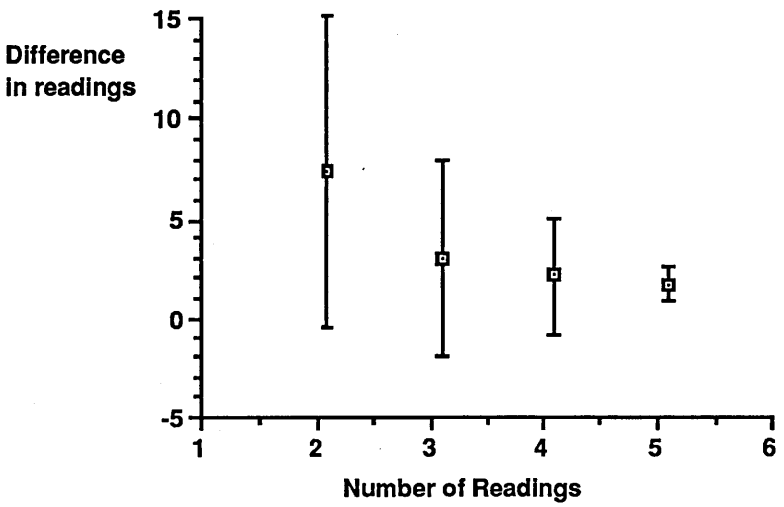


Figure 5.12

The differences in the consecutive averages of the diastolic blood pressures seen at Daycare. After the first three readings, adding a fourth reading does not significantly change the average result achieved (Values are mmHg±SD).

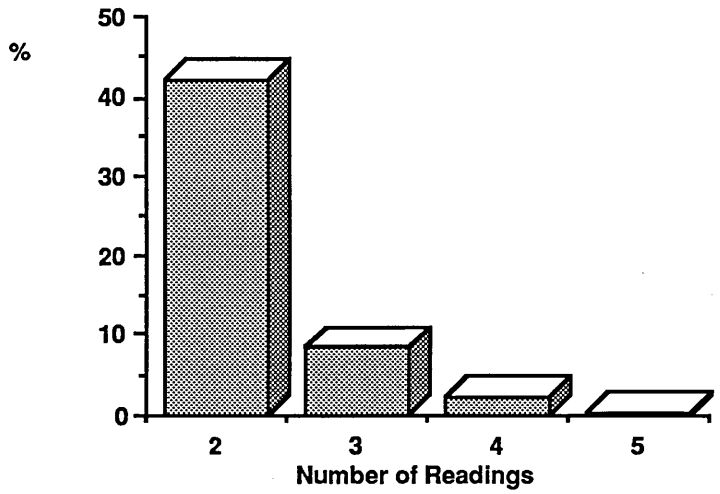


Figure 5.13

The percentage of patients with a difference between consecutive averages of more than 5 mmHg. Only 2% of the patients still had differences of greater than 5 mmHg between the averages of 3 and 4 readings. This implies that the average of 3 readings give accuracy in 98% of patients. The addition of a fourth reading improves this accuracy to almost 100%. A fifth reading does not appear to give any benefit.

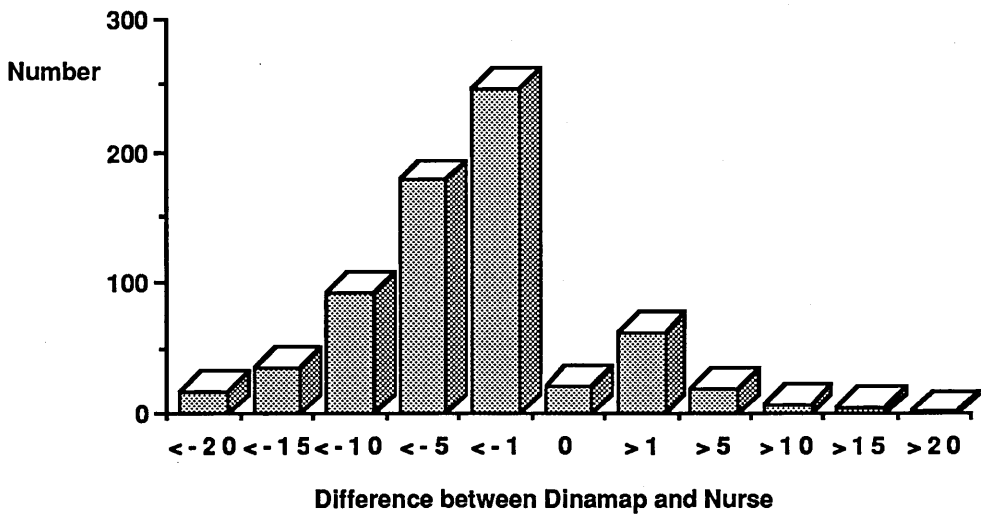


Figure 5.14

The incidence of the differences between the diastolic blood pressures found between the Dinamap and the nurse at Daycare. It can be seen that there are marked differences and most of the Dinamap readings are lower than the nurses readings. The average difference was 8.3±3.4 mmHg. This is probably related to the fact that the Dinamap is oscillatory and measures a diastolic blood pressure between somewhere between the fourth and fifth Korotkoff sounds.

The graph shows the cumulative number of patients were the difference was as stated. e.g. the first column shows the number of patients with a difference of greater than 20 mmHg, the next column shows the number of patients with a difference of greater than 15 mmHg, including those greater than 20 mmHg

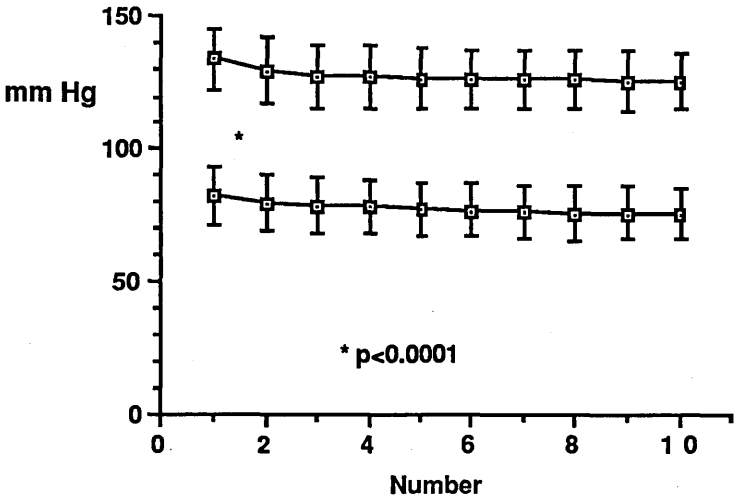


Figure 5.15

The trend in the 10 Dinamap blood pressure readings. There is a significant reduction from the first blood pressure readings to the rest (Values are mmHg±SD).

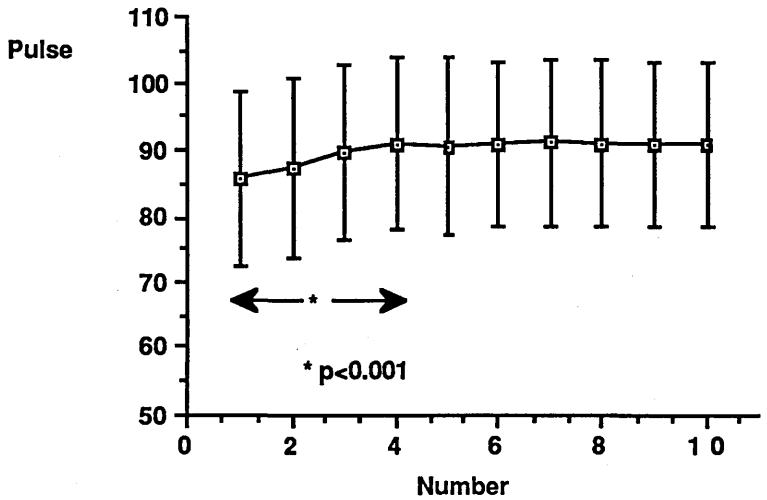


Figure 5.16

The trend of pulse rate over the ten Dinamap readings. There was no evidence that there was any anxiety at the beginning of the readings that would have explained the higher first BP reading. In fact, the pulse significantly rose over the first four readings. (Values are Heart Rate±SD)

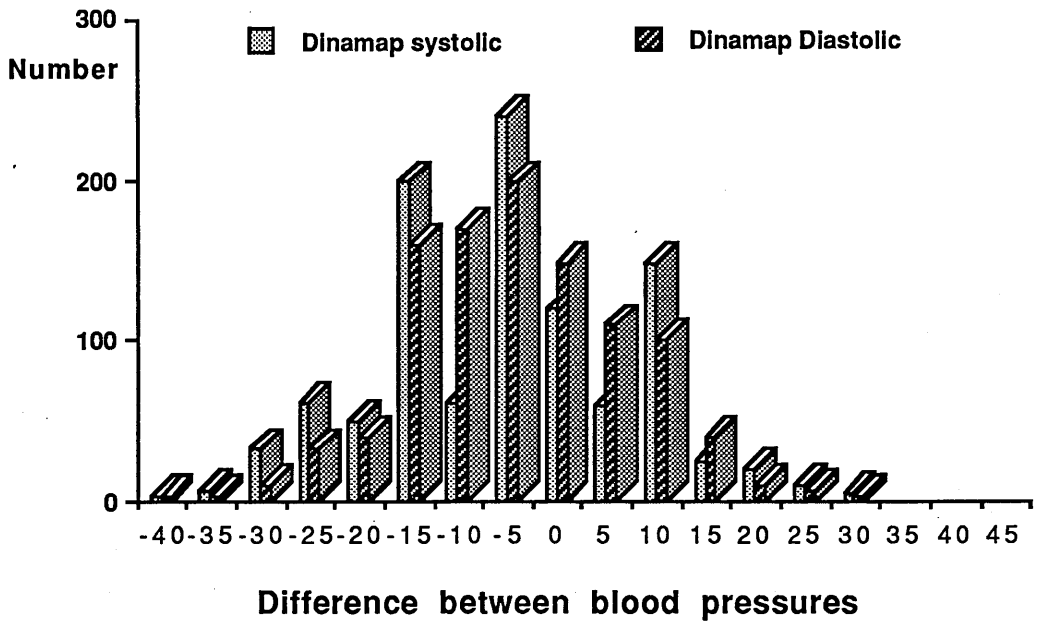


Figure 5.17

A graph showing the differences between the first two blood pressures readings taken in 1000 consecutive Daycare patients by the Dinamap blood pressure recorder. There was a wide variation in the consecutive readings and in less than 40% of the patients was the second blood pressure within 5 mmHg of the first. The difference could either be up or down.

Each column corresponds to the number of patients with a difference between the given figure and 4 mmHg above, e.g. the first column is the number of patients where the second reading is between 36-40 mmHg less than the first reading.

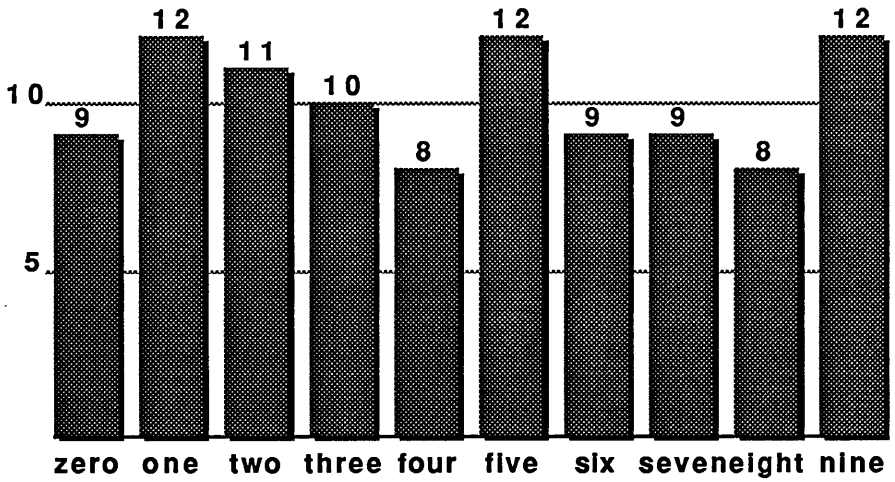


Figure 5.18

The incidence in percent of Diastolic blood pressure readings ending in the quoted digits in the combined group of the first and second Daycare readings by the Dinamap. As expected, there is no predominance for any given readings.

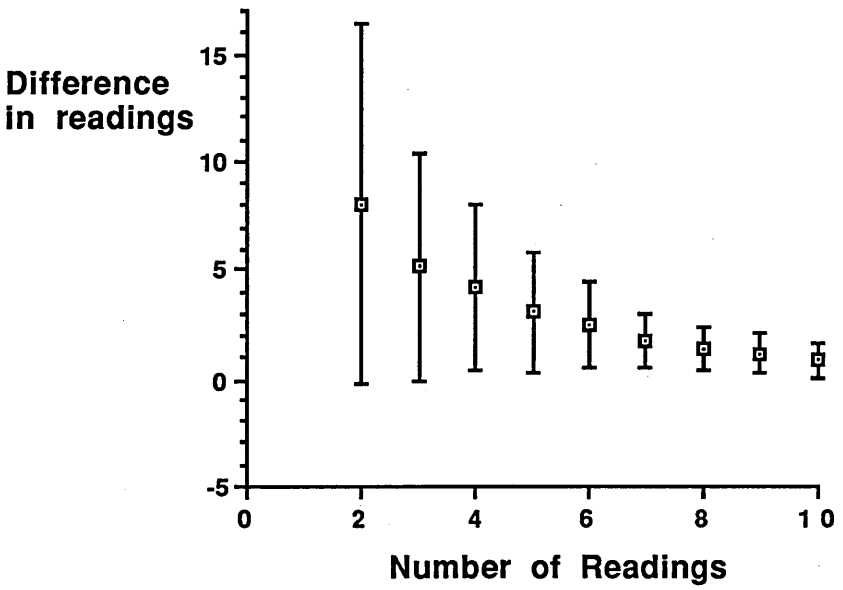


Figure 5.19

The differences in the consecutive averages of the diastolic blood pressures seen using the Dinamap. After the first six readings, adding a seventh reading does not significantly change the average result achieved. (Values are mmHg±SD)

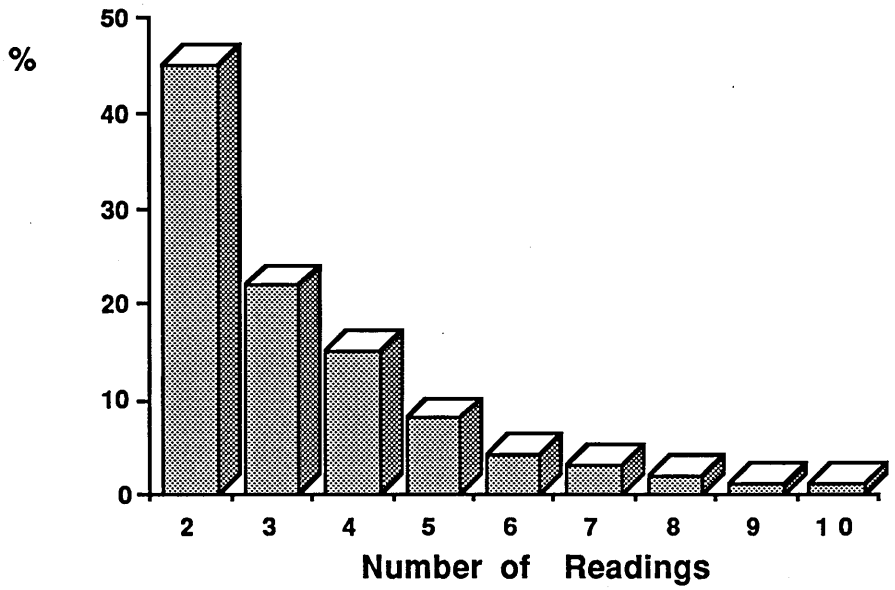


Figure 5.20

The percentage of patients with a difference between consecutive averages of more than 5 mmHg using the Dinamap. Only 3% of the patients still had differences of greater than 5 mmHg between the averages of 6 and 7 readings. This implies that the average of 6 readings using the Dinamap gives An accurate result in 97% of patients. The use of 8 readings improves this accuracy to almost 100%. A ninth or tenth reading does not appear to give any benefit.

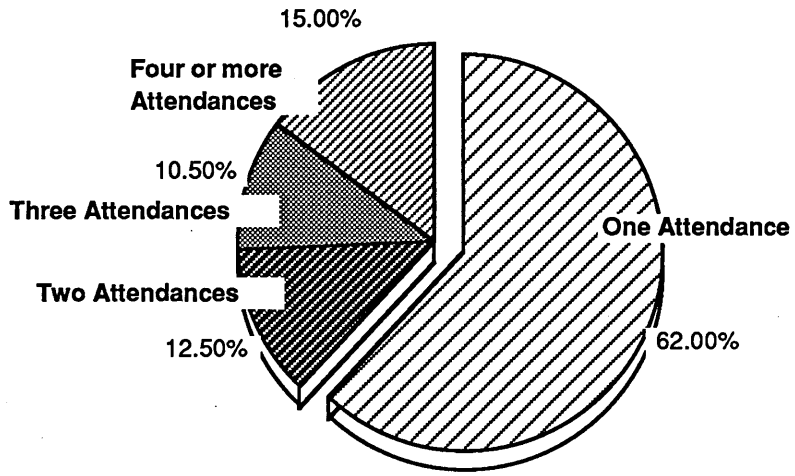


Figure 7.1

The number of attendances at Daycare. 62% had only one attendance. This is made up of those who are referred back to the Antenatal Clinic and a few that were admitted directly to hospital. The rest attended Daycare for further assessment.

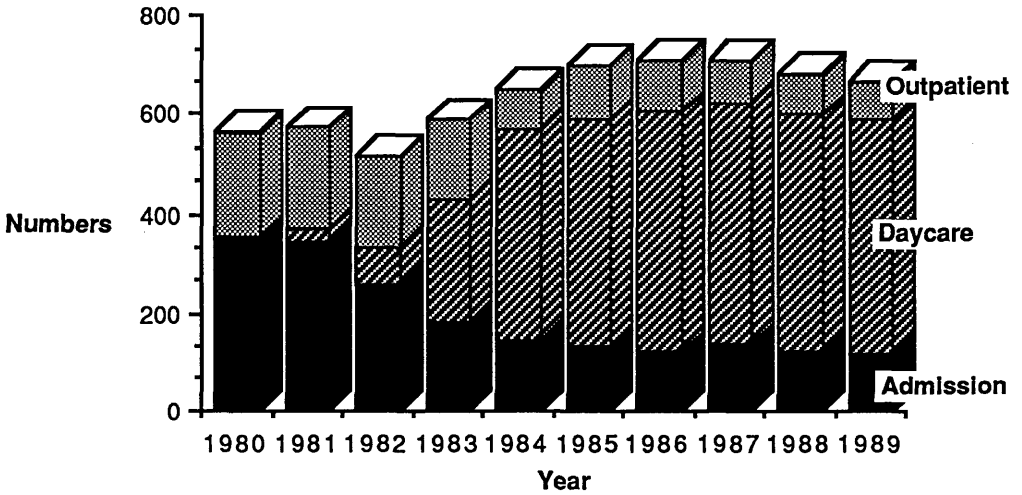


Figure 7.2

A graph of the number of admissions, Daycare Attendances and those managed at the normal outpatient clinic. Daycare has dramatically reduced the admissions to hospital but has led to an increased number that are monitored.

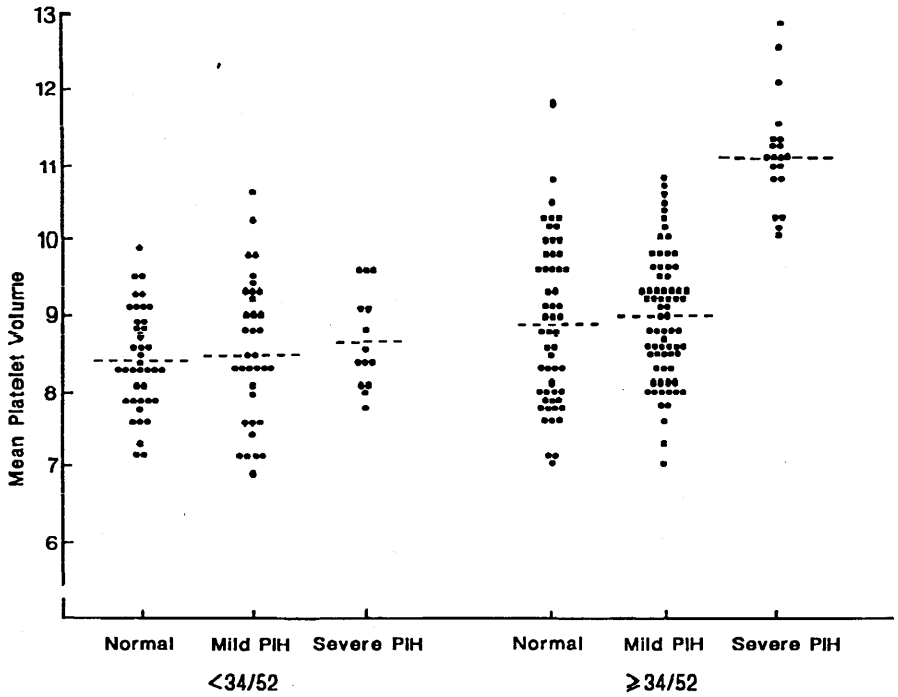


Figure 8.1

The changes in platelet size in normals, moderate pregnancy induced hypertension and severe disease. The increase in platelet size is only seen in the patients with late onset severe disease.

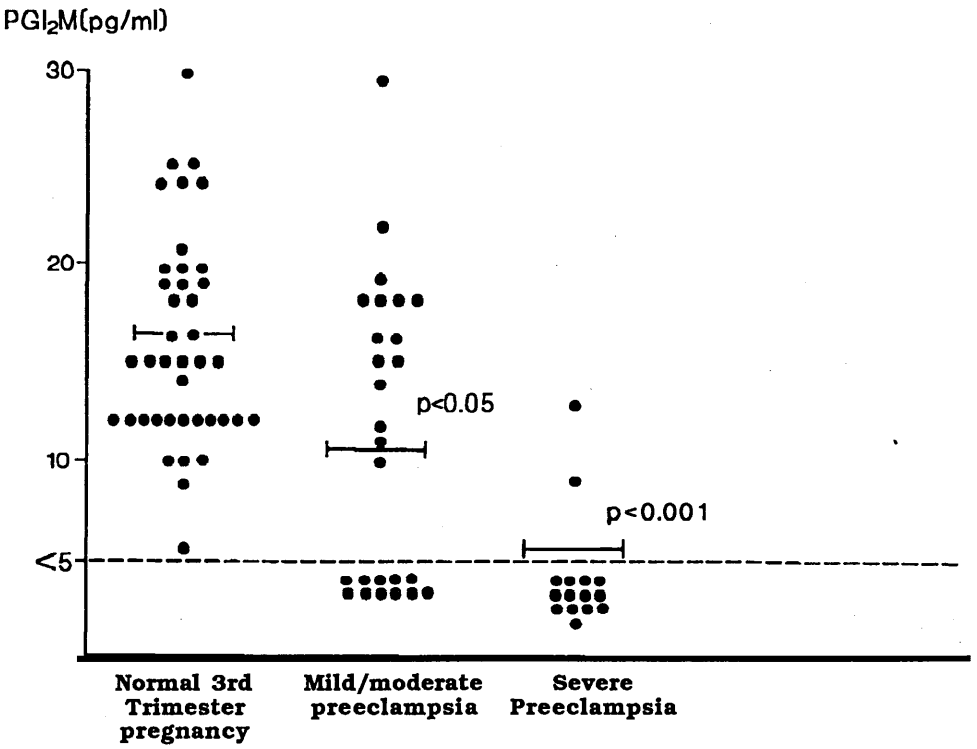


Figure 9.1

Prostacyclin levels in 40 normal third trimester pregnancies, 26 patients with moderate PIH (preeclampsia) and 15 patients with severe preeclampsia. Almost all severe and 50% of the moderate patients had prostacyclin levels below the measurable range.

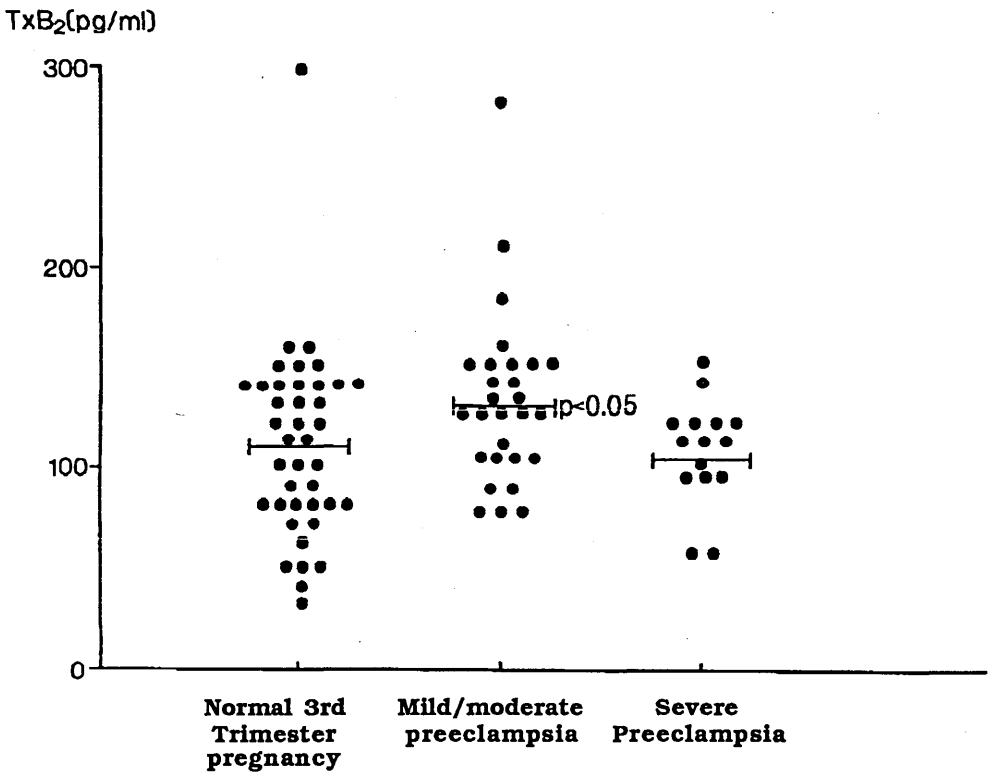


Figure 9.2

Thromboxane levels in 40 normal third trimester pregnancies, 26 patients with moderate PIH (preeclampsia) and 15 patients with severe preeclampsia. There was a significant increase in the moderate patients but no change in the severe patients who tended to present at an earlier gestation. This may well relate to the results seen in the platelet size studies where only in the milder late onset disease did platelet size increase.

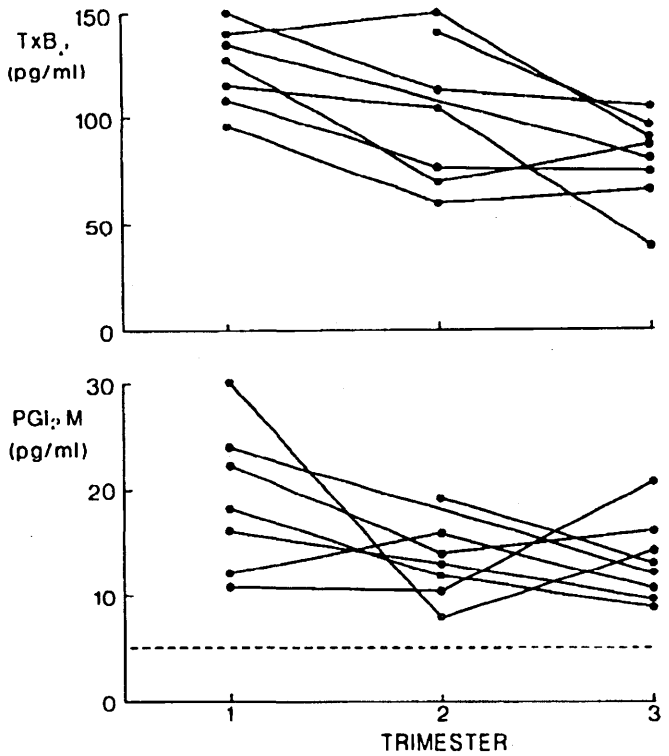
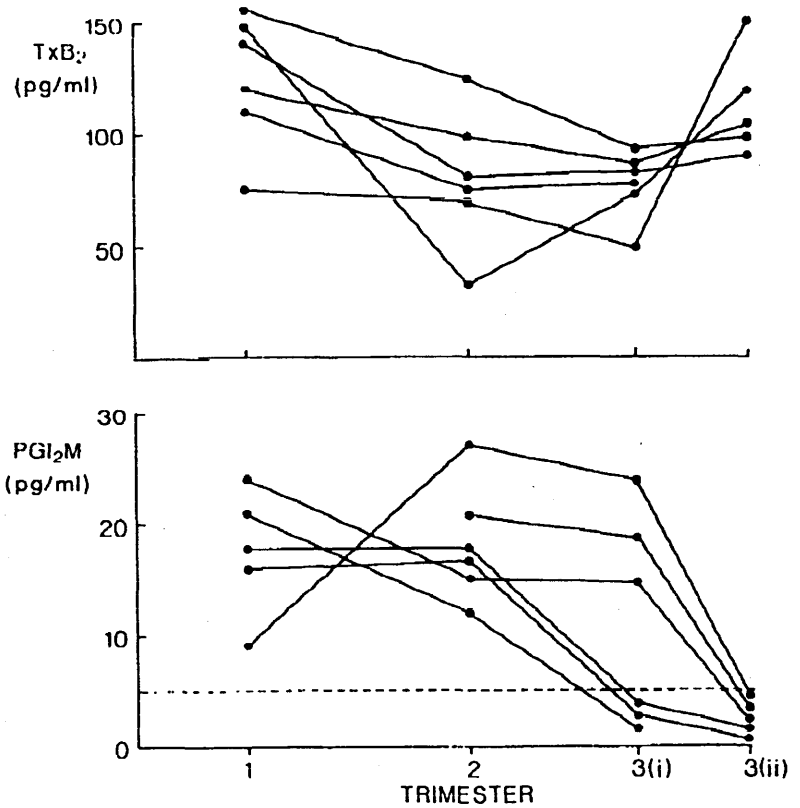


Figure 9.3

The serial changes in prostacyclin and thromboxane in those patients who remained normotensive. These results confirmed the cross-sectional study which showed elevated prostacyclin levels in early pregnancy, then falling with advancing gestation.



3 (i) = 32-36 weeks gestation **3 (ii)** = 37-40 weeks gestation

Figure 9.4

The serial changes in prostacyclin and thromboxane in those patients who developed pregnancy induced hypertension. The prostacyclin appeared to fall prior to the hypertension developing in half the patients. Thromboxane rose after development of the hypertension.

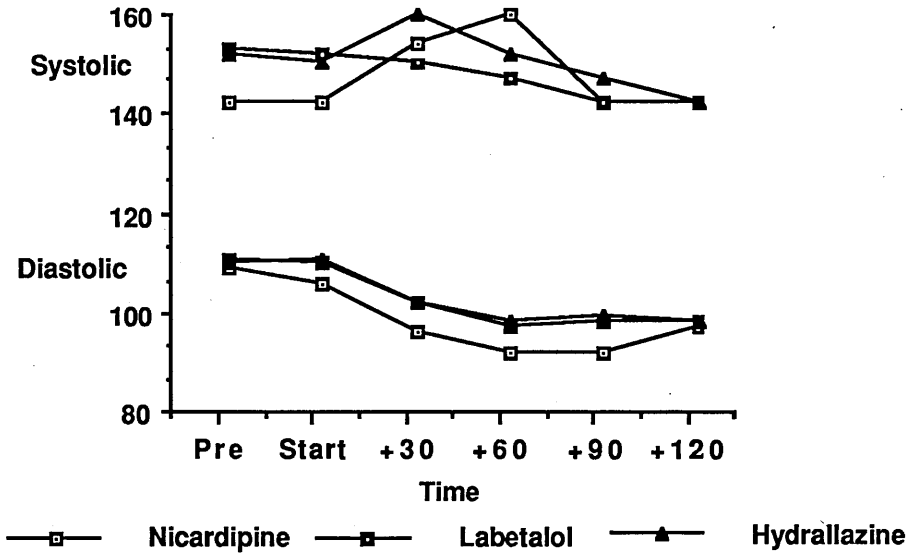


Figure 10.1

The effects of 200 mg labetalol, 10 mg oral nicardipine and 10 mg IM hydrallazine on hypertensive patients in pregnancy. All three drugs showed a statistically significant reduction in diastolic blood pressure by 30 mins which persisted for the rest of the two hour monitoring period ($p<0.001$) , Labetalol was the only drug to show a statistically significant reduction in systolic blood pressure at 60 minutes ($p<0.001$), but all had achieved a reduction by 2 hours ($p<0.001$).

(Wilcoxon rank sum test for matched pairs)

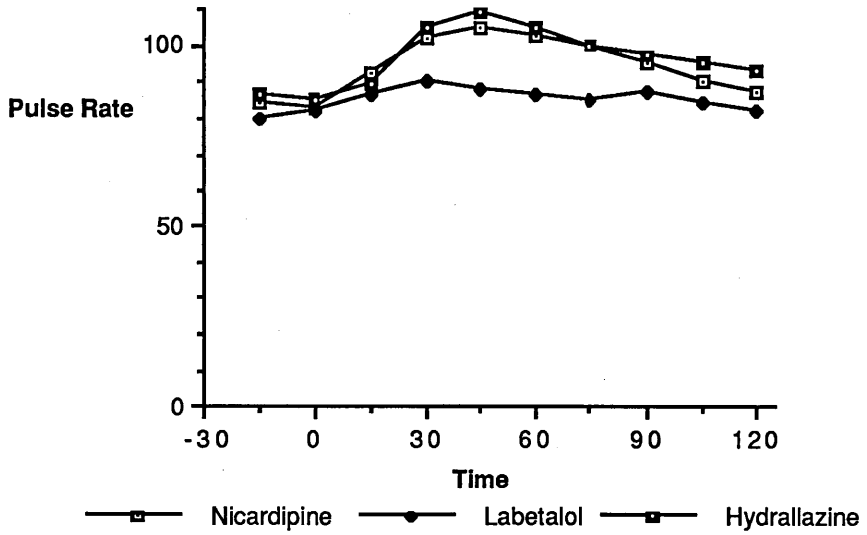


Figure 10.2

The pulse changes seen in the acute antihypertensive study. Both hydrallazine and nicardipine cause a tachycardia (Statistically significant between 30-60 minutes, $p<0.001$). Labetalol caused a small initial rise, but this did not reach statistical significance. There was no difference between the groups after 90 minutes.
(Wilcoxon Rank sum test for matched pairs)

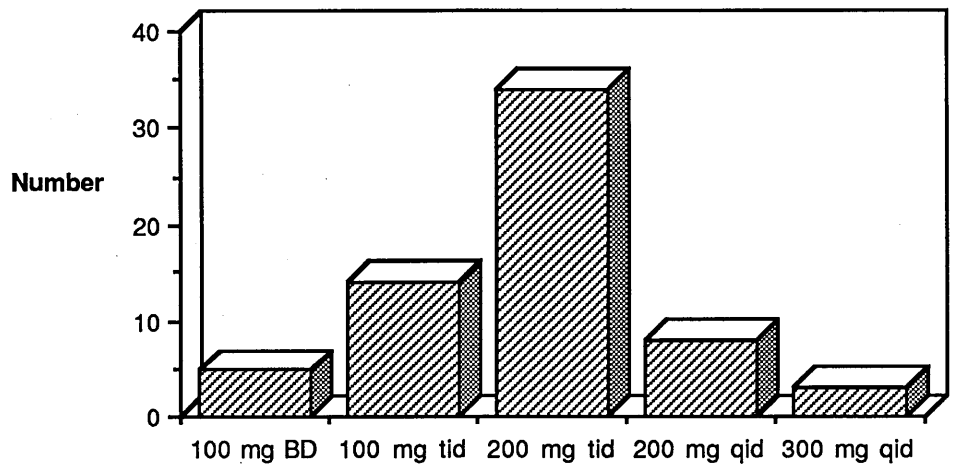
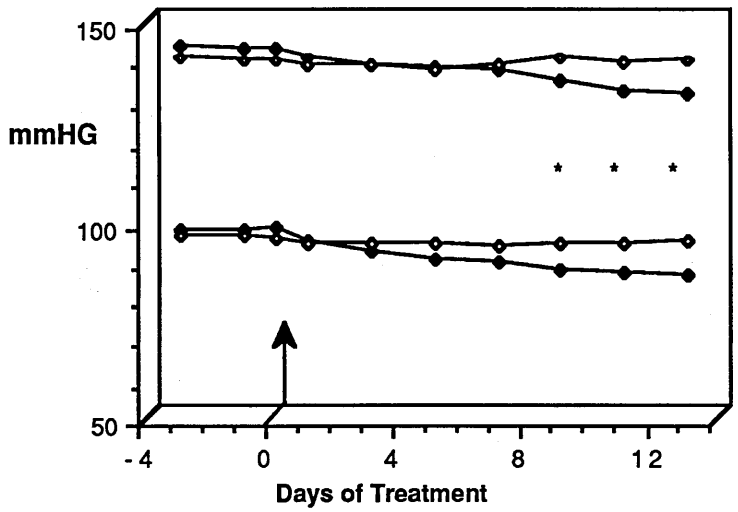


Figure 10.3

The number of patients controlled at given dose of labetalol. Few patients were controlled on 100 mg bd. Soon after the start of the study, the starting dose was raised to 200 mg tid as most patients appeared to require this amount to achieve adequate control.



***= p<0.01 between both Systolic and Diastolic Blood Pressures**

The open diamonds = the bed rest patients
The closed diamonds = the labetalol patients

Figure 10.4

The effect of labetalol on blood pressure. The systolic and diastolic blood pressures were found to be significantly reduced by day two in the treated group ($p<0.01$, Wilcoxon Rank Sum test) compared with pretreatment levels. However, no significant difference was found between the two groups until day nine of treatment (Mann Whitney U test).

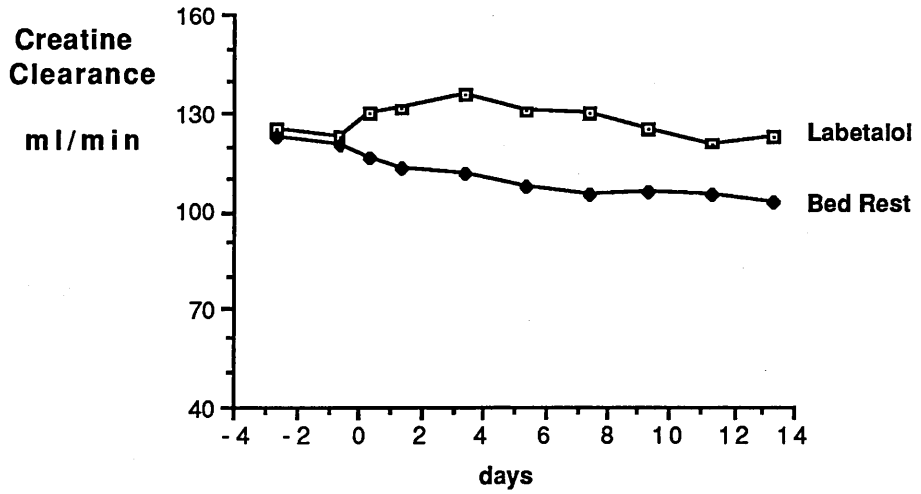


Figure 10.5

The changes seen in the creatinine clearance in the randomised mild/moderate study. This was a marked improvement seen in the first few days in the treated group. The difference between the treated and non-treated groups was statistically significant on days 3-7 ($p<0.005$). This difference was not maintained.

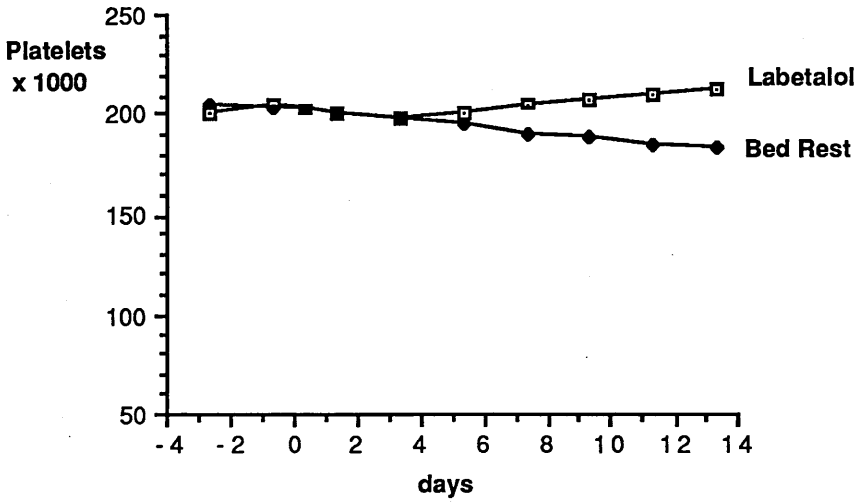


Figure 10.6

The platelet count in the randomised study. There was a small insignificant rise in the platelet count after commencement of labetalol. The platelet count fell in the untreated group. The difference reached significance after the seventh day of treatment ($p<0.005$).

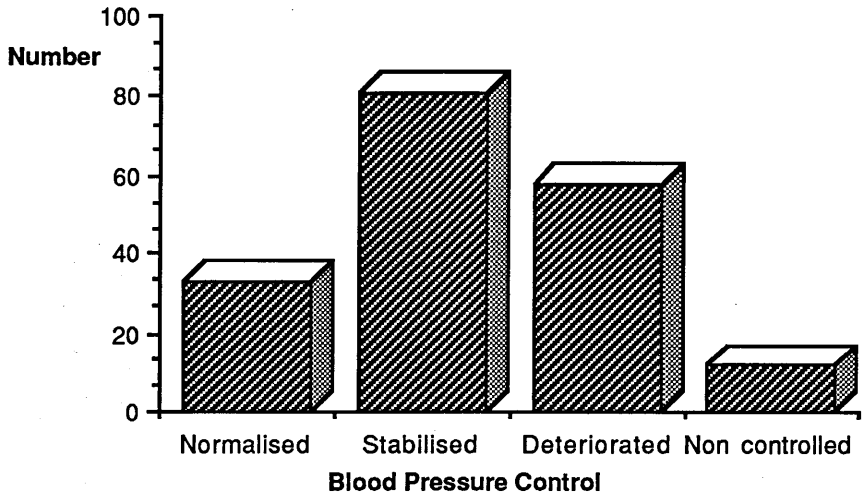


Figure 10.7

The number of patients who were controlled in the severe study. The majority settled into the normal range (less than 90 mmHg) or were stabilised (maintained between 90-100 mmHg). There were a small number of patients where control was not achieved, blood pressure rose further and delivery was necessary.

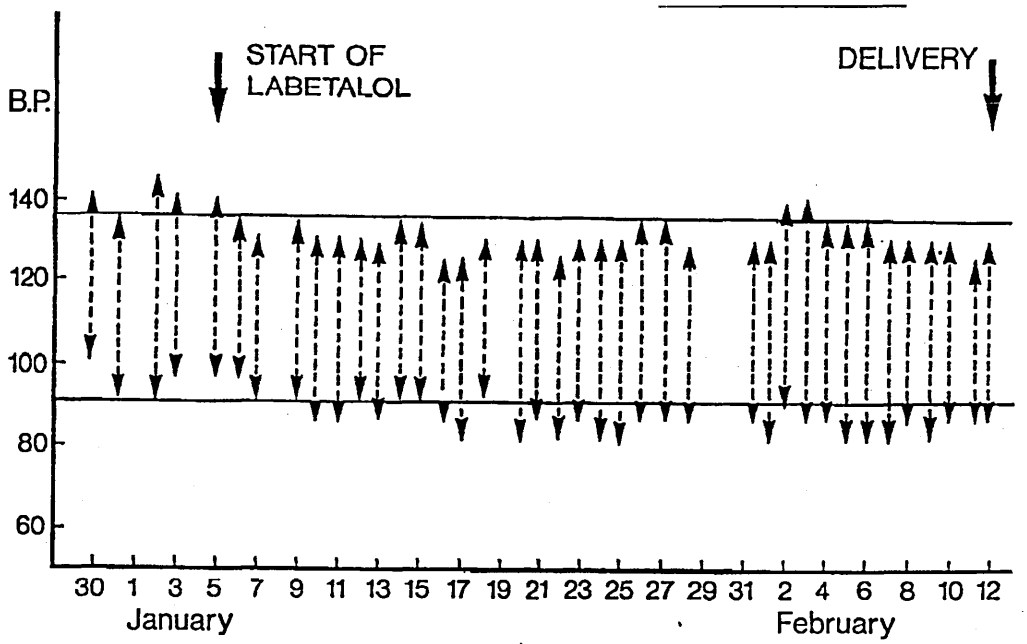


Figure 10.8

If blood pressure control is achieved with labetalol, long term control can be maintained and the patients can let home to return for Daycare management. The figure shows an random example of one patient where long term control was achieved. This is possible in around 20% of the patients.

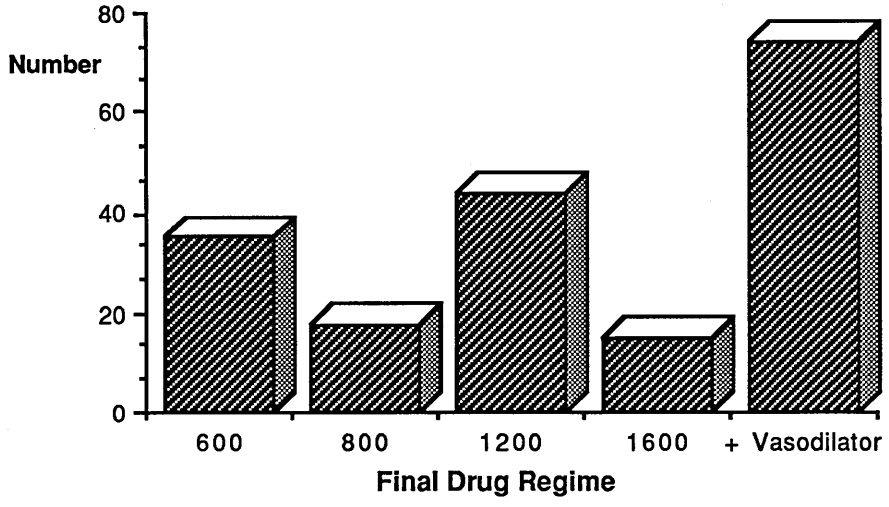


Figure 10.9

The final drug dosage and the incidence of the usage of vasodilators in the severe study. Over 40% of the patients were given vasodilators drugs as well as labetalol. In the majority of the cases, nifedipine was the vasodilator used.

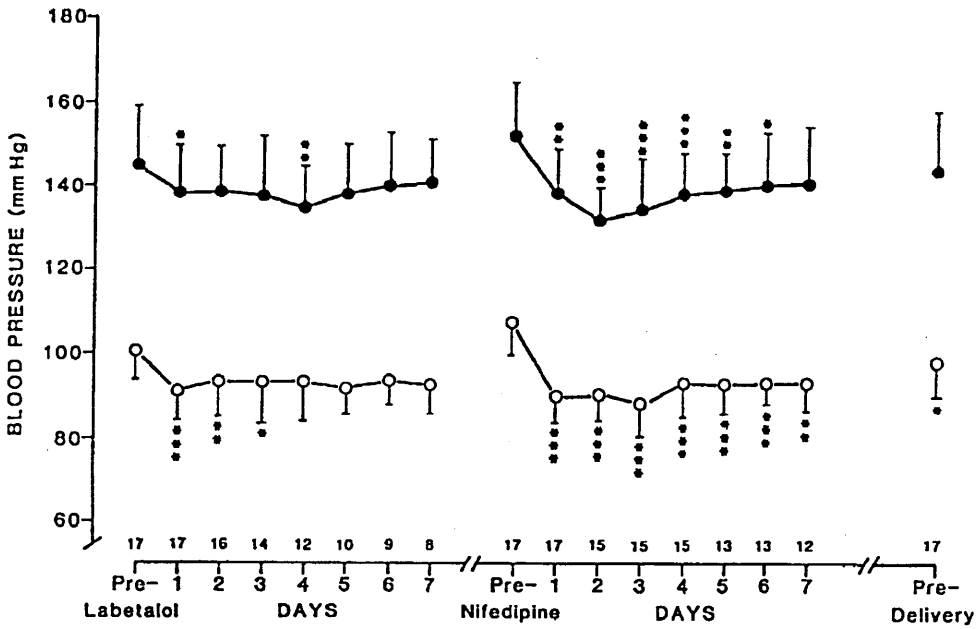


Figure 10.10

The effect of second line therapy with nifedipine. In patients where there is loss of control with labetalol alone, a further 7 days of control can often be achieved.

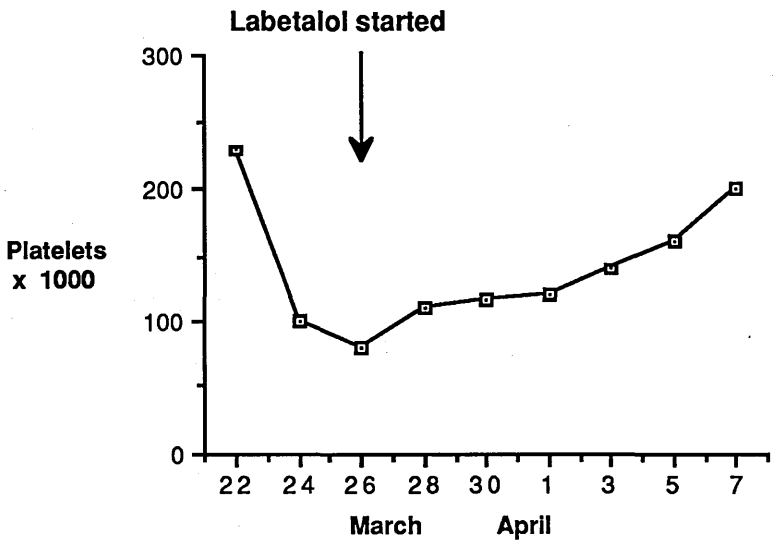


Figure 10.11

The effect of labetalol on the platelet count in a single patient. Not all the patients had such a dramatic response, but the platelet count tended to improve after labetalol was commenced.

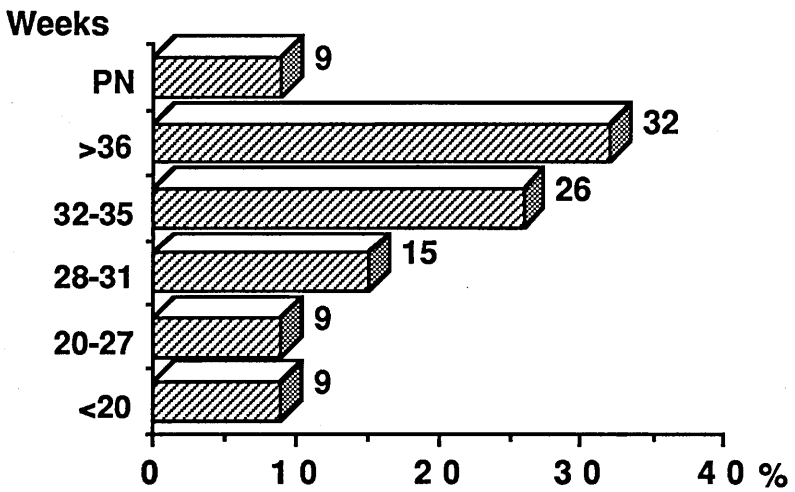


Figure 10.12

The gestation at presentation of all those seen at the GRMH with hypertension in pregnancy. Most of the patients are between 32-40 weeks. These patients are easy to manage as the delivery option is available. A significant number of the patients present below 32 weeks. These are the patients that would benefit most from intervention therapy.

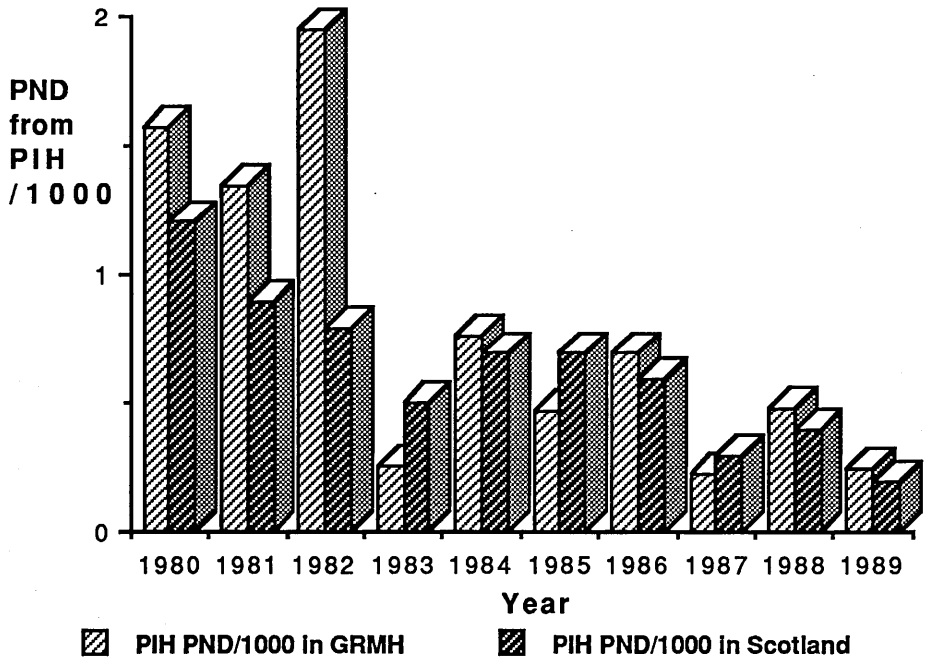


Figure 10.13

The PND associated with hypertension per 1000 of all deliveries in the Glasgow Royal Maternity Hospital and in Scotland for the years 1980-89. For the years 1980-82, the rates in GRMH were higher than for Scotland, but there has been no difference in the years since.

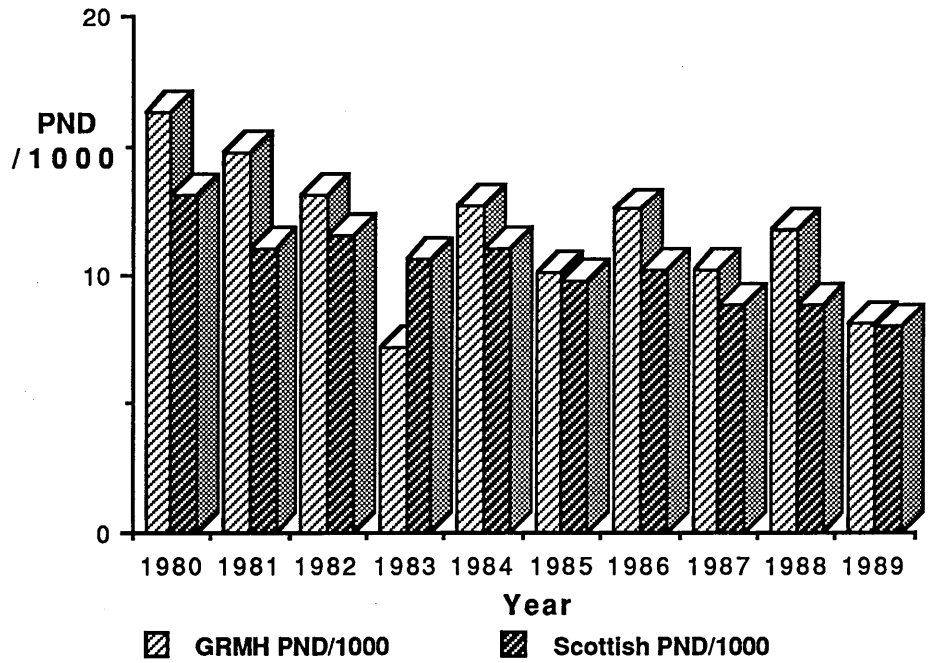


Figure 10.14

The PND in the Glasgow Royal Maternity Hospital and in Scotland for the years 1980-89. In the all years apart from 1983, the rate for GRMH have been higher than that in Scotland as a whole ($p<0.001$)

(Wilcoxon rank sum test)

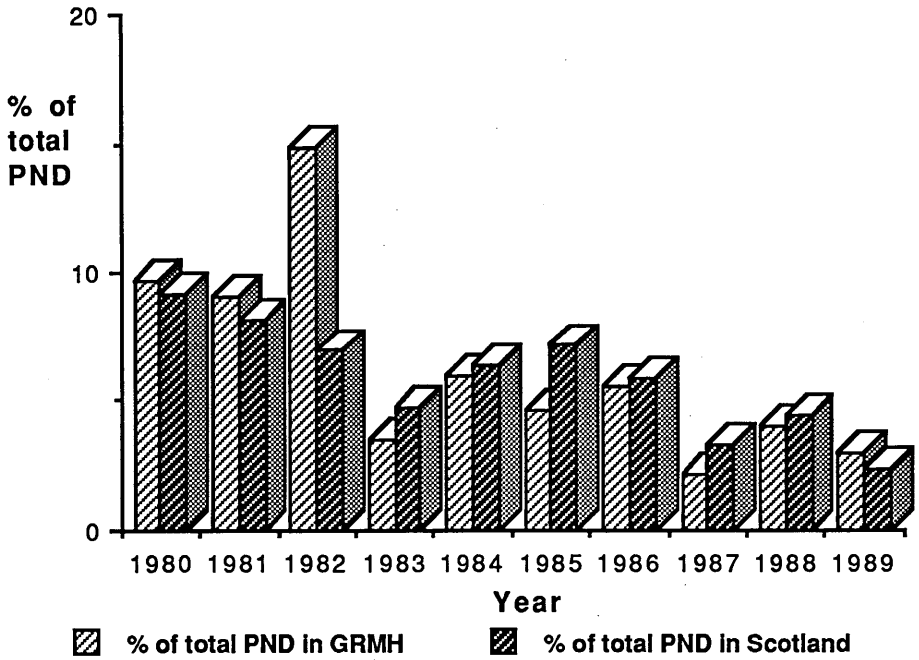


Figure 10.15

The percentage of the total PND that were associated with hypertension in the Glasgow Royal Maternity Hospital and in Scotland for the years 1980-89. In the years 1980-82 the rates were higher in GRMH, but in the years 1983-89, the percentage for GRMH has been significantly less than for the rest of Scotland ($p<0.01$)

(Wilcoxon Rank sum test)

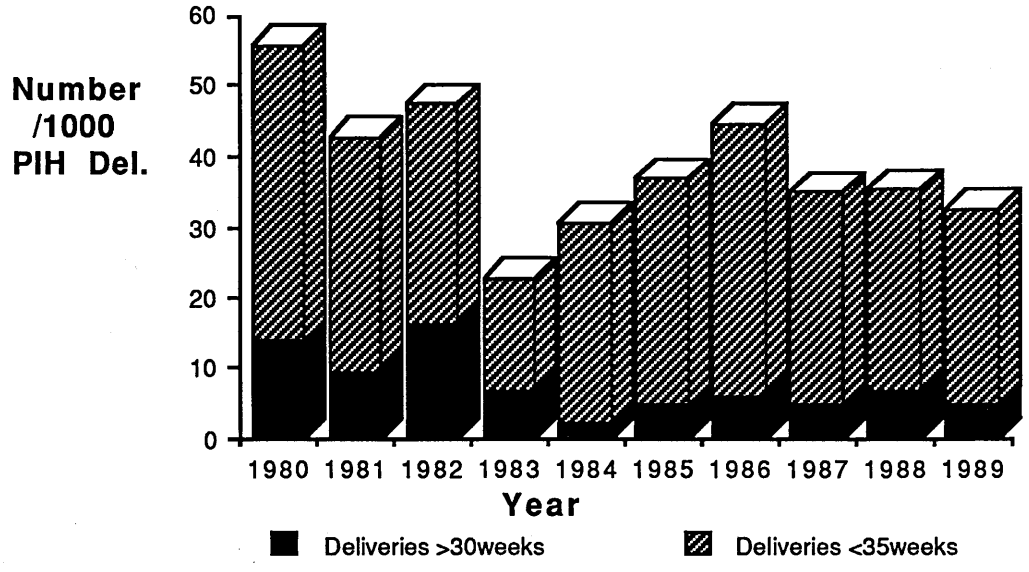


Figure 10.16

The incidence of delivery under 35 and 30 weeks in pregnancies in GRMH booked patients affected by hypertension in pregnancy. Figures are shown for number of deliveries per 1000 hypertensives in the hospital per year. There was an improvement around 1983 with a reduction in deliveries less than 30 weeks. If the years 1980-82 are compared with 1983-1989, the rate of delivery less than 30 weeks has significantly reduced ($p<0.005$). There has also been a small but significant change in the rate under 35 weeks ($p<0.05$).

(Fishers exact test)

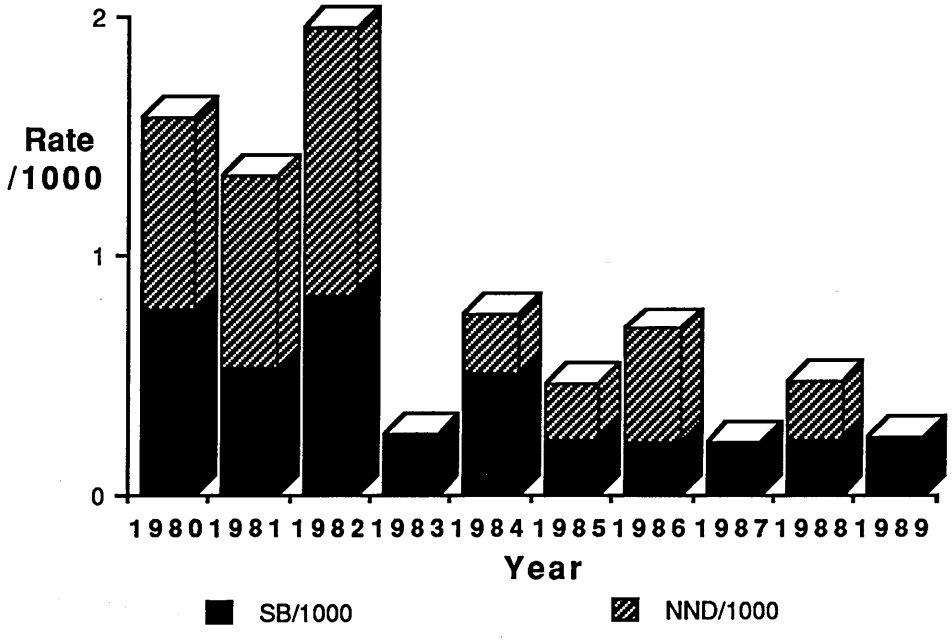


Figure 10.17

A graph of the changes in the stillbirth and neonatal death rates per 1000 of all deliveries in GRMH booked patients associated with hypertension in pregnancy. When compared with the rates for 1980-82, there has been a significant reduction for both stillbirth ($p<0.05$) and neonatal death ($p<0.005$) in the years 1983-89. The reduction in overall perinatal death rate is also significantly reduced ($p<0.001$) (Fishers exact test)

The Daycare Programme

The Daycare Programme

The basis of good research is documentation. From the very beginning of these studies, I used computers to store data in a form that would allow easy analysis. The development of these systems was an integral part of the work. It allowed the collection and evaluation of a large amount of data. The initial computers used were BBC microcomputers with attached disc drives. There was no database available that appeared to be able to serve our purposes. I then decided to write my own programmes for the computers. These were all written in BBC Basic, a high level structured language with procedures and functions. It has particularly good file handling and colour graphic capabilities. There was three main programmes written; the Daycare programme, the Platelet size database and the Dinamap interface programme. There were many other smaller programmes written to collect data, analysis the files and finally to transfer the data into IBM compatible Dbase files or Mac compatible FileMaker files. This allowed an upward compatibility of the databases with the improvement of the computer facilities as the more more powerful machines became available.

Listed below is the Daycare programme. This was the mainstay of the hypertensive database allowing storage of data on the thousands of attendances through the Daycare unit. This programme was designed, developed and written totally by the author.

The Daycare Programme

```
 0 REM DAYCARE PROGRAM
 1 REM Copyright JJ WALKER 1990
10 ONERRORGOTO30000
20 MODE 7
30 PROC_DATA
40 PROC_INFO
90 REPEAT
95  axes%=0:gotit%=0
100  ANS$=FN_MENU(12330)
120 IF ANS$="S" THEN PROC_SPECIAL
121 IF ANS$="1" THEN PROC_NEW
122 IF ANS$="2" THEN PROC_ENDOFDAY
123 IF ANS$="3" THEN PROC_AXESFIL:ANS$=""
124 IF ANS$="4" THEN PROC_LIST
125 IF ANS$="5" THEN PROC_GESTATION
126 IF ANS$="6" THEN PROC_DATECHANGE
127 IF ANS$="7" THEN  PROC_TIME
130 UNTIL ANS$="E" OR ANS$="8"
140 PROC_SAVECURRENT
145 IF ANS$="8" THEN CHAIN"PATCHCK"
150 END
160 :
170 DEFPROC_SPECIAL
171 LOCAL ANS$
172 CLS
174  pw$=""
```

```
 176 PROC_DH(5,2,CHR$129+"THIS IS THE SPECIAL FUNCTIONS")
 178 PROC_DH(5,6,CHR$129+"WHAT IS THE PASSWORD ?")
 180  A$=GET$:pw$=pw$+A$
:PROC_DH(5,10,CHR$130+STRING$(LENpw$,"*")):IF  LENpw$<5  THEN  180
 182 IF pw$<>"JIMMY" THEN ENDPROC
 184 REPEAT
 185  ANS$=FN_MENU(12331)
 186 IF ANS$="1" THEN PRINT"1) ERASE CURRENT FILE Y/N?":A$=GET$:IF
A$="Y" THEN PROC_ERASE
 188 IF ANS$="2" THEN PRINT"2) ERASE LAST DATE Y/N?":A$=GET$:IF A$="Y"
THEN PROC_ERASEDATE
 190 IF ANS$="3" THEN INPUT"Ram No ";ram%
 192 IF ANS$="4" THEN axes%=0:PROC_ERASEPATIENT:RUN
 194 UNTIL A$="E"
 196 ENDPROC
 198 :
 200 DEFFN_MENU(restore%)
 202 RESTORE restore%
 205 READ ADD$,num%
 210 PROC_HEAD
 215 FOR quest%=1 TO num%
 217 READ quest$
 220  PROC_DH(5,quest%*2,CHR$129+STR$quest%+")  "+quest$)
 230 NEXT
 240 READ answer$
 250 =FN_ANSWER(answer$)
 290 :
 300 DEFPROC_NEW
 310 CLS:IF TDDATE$<>"00/00/00" THENPROC_DISPLAY:ENDPROC
 315 ADD$="DATE INPUT":PROC_HEAD
 320 IFTDDATE$="00/00/00" THEN PROC_DH(0,1,CHR$130+"CURRENT FILE
EMPTY")
 330 PROC_DH(0,1,CHR$130+"CURRENT FILE CONTAINS "+TDDATE$)
 340 IF D%=0 THEN PROC_DH(0,4,CHR$129+"INPUT DAYS DATE (00/00/00)")
 350 TDDATE$=FN_DATE(21,7,85,86):D%=FN_CALCDATE(TDDATE$)
 355 PROC_DISPLAY
 360 ENDPROC
 370 :
 400 DEFPROC_DATECHANGE
 410 CLS
 415 PROC_DH(3,3,"ÅPRESENT DATE IS "+TDDATE$)
 420 PROC_DH(3,5,"ÇINPUT NEW DATE")
 450 TDDATE$=FN_DATE(21,7,85,86):D%=FN_CALCDATE(TDDATE$
:PROC_SAVECURRENT
 460 ENDPROC
1000 DEFPROC_BASICDATA
1010 CLS:ADD$="BASIC DATA":HEAD$="D/C "+TDDATE$:PROC_HEAD
1020  miss%=0:change%=0:alr%=0:first%=1
1030  PROC_DH(0,0,CHR$129+"PATIENT  "+STR$(P%+1))
1040  PRINTTAB(0,2);"NAME  (A  SMITH)"
1045  IFNAME$(P%)<>STRING$(15,"  ")THENPRINTTAB(20,2)NAME$(P%);
:gg%=1:first%=0
1050  IFNAME$(P%)<>STRING$(15,"  ")THENPRINTTAB(20,2)NAME$(P%);
:GOTOFN_OK(1060,1070)
1060  NAME$(P%)=FN_NAMEINPUT(20,2)
1070  PRINTTAB(0,4);"UNIT  NUMBER  "
1080  IFVAL(UNIT$(P%))<>0THENPRINTTAB(20,4)UNIT$(P%);:GOTO1090
```

```
 1085  UNIT$(P%)=FN_INPUT(20,4,6,num$)
 1090  PRINTTAB(35,4);:GOTOFN_OK(1085,1100)
 1100  IFLEN(UNIT$(P%))=5  THEN  UNIT$(P%)="  "+UNIT$(P%)
 1110 IF change%=0 AND miss%=0 AND VALDOB$(P%)=0 THENPROC_ALREADY
ELSE GOTO1130
 1112  IF  alr%=1  THEN  first%=0
 1120 miss%=1:GOTO 1080
 1130 PRINTTAB(0,6);"DATE OF BIRTH"
 1140  IFVAL(DOB$(P%))<>0THENPRINTTAB(20,6);DOB$(P%);
:GOTOFN_OK(1145,1150)
 1145  DOB$(P%)=FN_DATE(20,6,40,75)
 1150  PRINTTAB(0,8);"PARITY  (0+0)";TAB(20,8);PARITY$(P%);
:GOTOFN_OK(1160,1190)
 1160  PARITY$(P%)=FN_INPUT(20,8,3,num$+"+")
 1170  IFLEN(PARITY$(P%))<>3  OR  MID$(PARITY$(P%),2,1)<>"+"THEN1160
 1180  GOTOFN_OK(1160,1190)
 1190  PRINTTAB(0,10);"LMP  "
 1200  IFVAL(LMP$(P%))<>0THENPRINTTAB(20,10);LMP$(P%);
:GOTOFN_OK(1205,1210)
 1205  LMP$(P%)=FN_DATE(20,10,85,86)
 1207 IF VALGEST$(P%)>0 THEN GOTO 1220
 1210  GEST$(P%)=FN_GEST(LMP$(P%),TDDATE$)
:EDD$(P%)=FN_CALCEDD(LMP$(P%),0,VALRIGHT$(TDDATE$,2))
 1220 IF VALGEST$(P%)>44 OR VALGEST$(P%)<4 THEN VDU7
:PRINTTAB(28,10)"WRONG":GOTOFN_OK(1230,1205)
 1230  PRINTTAB(0,12);"EDD  "
 1240  IFVALEDD$(P%)<>0  THENPRINTTAB(20,12);EDD$(P%);
:GOTOFN_OK(1250,1260)
 1250  EDD$(P%)=FN_DATE(20,12,85,86)
 1260 PRINTTAB(0,14);"GESTATION  "
 1270  IFVALGEST$(P%)<>0THENPRINTTAB(20,14);GEST$(P%);
:GOTOFN_OK(1275,1280)
 1275  GEST$(P%)=FN_INPUT(20,14,2,num$):GOTOFN_OK(1275,1280)
 1280 PRINTTAB(0,16)"WHICH ATTENDANCE"
:IFVAL(ATTNO$(P%))<>0THENPRINTTAB(20,16);ATTNO$(P%);:alr%=1
:GOTOFN_OK(1290,1300)
 1290  ATTNO$(P%)=FN_INPUT(20,16,2,num$):GOTOFN_OK(1290,1300)
 1300 PRINTTAB(5,18)"ARE THESE CORRECT ?";:gg%=0:GOTOFN_OK(1310,1320)
 1310 change%=1:GOTO1050
 1320 change%=0:
 1325 IF ATTNO$(P%)="1" AND first%<>1 THEN alr%=1
 1327 IF ATTNO$(P%)="1" AND first%=1 THEN alr%=0
 1328 IF alr%=1 THEN gg%=1 ELSE gg%=0
 1330 PROC_DISPLAY1
 1340 IFalr%=1 OR change%=1 THENGOTO1375
 1350 CLS:PRINTTAB(0,1);"CONSULTANT  "
 1360  FORD%=0  TO  7:PRINTTAB(20,(1+D%));D%;")  ";CONS$(D%):NEXT
 1370  CON$(P%)=FN_ANSWER("01234567")
 1375  VDU28,0,24,39,6
 1380 CLS:PRINTTAB(0,1);"CONSULTANT  ";TAB(20);CONS$(VAL(CON$(P%)));
:GOTOFN_OK(1350,1390)
 1390  VDU28,0,24,39,9
 1400  PRINTTAB(0,1);"Source";TAB(0,3)"of  referal"
 1410 IFalr%=1 OR change%=1 THEN1430
 1420  FOR  D%=0  TO  3:PRINTTAB(18,(1+(D%*2)));D%;")";REF1$(D%):NEXT
:REFERAL$(P%,1)=FN_ANSWER("0123")
 1425  VDU28,0,24,39,9
```

```
1430 CLS:PRINTTAB(0,1);"Source of referal ";TAB(18,1)
;REF1$(VAL(REFERAL$(P%,1)));:GOTOFN_OK(1420,1440)
1440  VDU28,0,24,39,11
1450 IFalr%=1 OR change%=1 THEN1480
1460  PRINTTAB(0,1);"Reason";TAB(0,3)"for  referal"
1470 FOR D%=0 TO 5:PRINTTAB(14,(1+D%));D%;")";REF2$(D%):NEXT
:REFERAL$(P%,2)=FN_ANSWER("012345")
1475  VDU28,0,24,39,11
1480 CLS:PRINTTAB(0,1);"Referal Reason";TAB(15,1)
;REF2$(VAL(REFERAL$(P%,2)));:GOTOFN_OK(1470,1490)
1490  VDU28,0,24,39,13
1500 PRINTTAB(0,1);"Referal Date"
1510 IFVALREFDATE$(P%)<>0 THENPRINTTAB(20,1);REFDATE$(P%);
:GOTOFN_OK(1520,1530)
1520  REFDATE$(P%)=FN_DATE(20,1,85,86)
:IF VALLEFT$(FN_GEST(REFDATE$(P%),TDDATE$),2)<0 THEN VDU7
:PRINTTAB(28,1)"WRONG":GOTOFN_OK(1530,1520)
1530 PRINTTAB(0,3);"Referal BP "
1540 IFVALREFBP$(P%)<>0 THENPRINTTAB(20,3);REFBP$(P%);
:GOTOFN_OK(1545,1550)
1545  REFBP$(P%)=FN_BP(20,3)
1550 PRINTTAB(0,5);"Booking BP"
1560 IFVALBKBP$(P%)<>0 THENPRINTTAB(20,5);BKBP$(P%);
:GOTOFN_OK(1565,1570)
1565  BKBP$(P%)=FN_BP(20,5)
1570 PRINTTAB(0,6);"Booking Gestation"
1580 IFVALBKGEST$(P%)<>0THENPRINTTAB(20,6);BKGEST$(P%);
:GOTOFN_OK(1590,1600)
1590  BKGEST$(P%)=FN_INPUT(20,6,2,num$)
:IF VALBKGEST$(P%)>VALGEST$(P%) THEN 1590 ELSE GOTOFN_OK(1590,1600)
1600 PRINTTAB(0,8);"BP AT 28/30 WKS"
1610 IFalr%=1 OR VALGEST$(P%)<28 THENPRINTTAB(20,8);BP28$(P%);
:GOTOFN_OK(1620,1630)
1620  BP28$(P%)=FN_BP(20,8)
1630 PRINT'TAB(5)"ARE THESE CORRECT ?";:gg%=0:GOTOFN_OK(1640,1650)
1640 change%=1:GOTO1340
1650 IF axes%=0 THEN PROC_SAVECURRENT
1655 IF axes%=1 THEN PROC_SAVE
1660  VDU28,0,24,39,3:CLS
1670 ENDPROC
1680  :
2000 DEFPROC_DINAREADINGS
2010 ENDPROC
4000 DEFPROC_ENDOFDAY
4030 PROC_ENDMENU
4040 IF ANS$="1" THEN PROC_PRINT
4050 IF ANS$="2" THEN PROC_NEXT:ENDPROC
4060 IF ANS$="3" OR ANS$="E"THENANS$="":ENDPROC
4070 GOTO4030
4080 DEFPROC_ENDMENU
4085 MODE 7:ADD$="END OF DAY":HEAD$="DAYCARE":PROC_HEAD
4090 PROC_DH(5,4,CHR$129+"1) PRINT RECORD SHEETS")
4100 PROC_DH(5,6,CHR$129+"2) CLOSE TODAYS FILE")
4110 PROC_DH(5,8,CHR$129+"3) RETURN TO DAYCARE PROGRAM")
4120  ANS$=FN_ANSWER("1234")
4130 ENDPROC
4140  :
```

```
4150 DEFPROC_NEXT
4160 PROC_DOWNLOAD
4170 PROC_CLEARCURRENT
4175  ok%=1
4180 PROC_SAVECURRENT
4200 MODE 7:RUN
4201 DEFPROC_ERASE
4205 GOTO4170
4206 DEFPROC_ERASEDATE
4207  DAT%=OPENUP("DTINX88")
4208  INPUT#DAT%,DATinput%,DATlength%
4209  PTR#DAT%=0
4210  DATinput%=DATinput%-DATlength%
4211  PRINT#DAT%,DATinput%
4212 CLOSE#DAT%
4213 ENDPROC
4215 ENDPROC
4220 DEFPROC_DOWNLOAD
4230  FILE$=LEFT$(TDDATE$,2)+MID$(TDDATE$,4,2)+RIGHT$(TDDATE$,2)
4235 FOR dr%=0 TO 4 STEP 4
4240  DAT%=OPENUP(":"+STR$dr%+".DTINX88")
4250  INPUT#DAT%,DATinput%,DATlength%
4260  PTR#DAT%=DATinput%-DATlength%
4270  INPUT#DAT%,date$
:IF date$=RIGHT$(FILE$,6) THEN PRINT"DATA ALREADY DOWNLOADED":GOTO4430
4275 IF dr%=0 THEN fdr%=2 ELSE fdr%=5
4280  ATT%=OPENUP(":"+STR$fdr%+".DC/FL88")
4290  INPUT#ATT%,input%,length%
4300  PTR#DAT%=DATinput%
4310  PRINT#DAT%,RIGHT$(FILE$,6),input%
4315 CLS
4316   P%=-1
4320 REPEAT
4322  P%=P%+1
4325 PROC_DH(5,5,"ÅDOWNLOADING PATIENT "+STR$(P%+1))
4330  PTR#ATT%=input%
4340 PROC_BPUT
4350  input%=input%+length%
4360 UNTIL P%=8 OR LEFT$(NAME$(P%+1),3)="    "
4370  last%=input%-length%
4380  PRINT#DAT%,last%
4390  DATinput%=PTR#DAT%:PTR#DAT%=0
4400  PRINT#DAT%,DATinput%
4410  PTR#ATT%=0:PRINT#ATT%,input%
4415 NEXT
4420 CLOSE#0
4430  :
4440 ENDPROC
4450  :
4500 DEFPROC_INDEX
4510  DAT%=OPENUP("DTINX88")
4520  ATT%=OPENUP(":2.DC/FL88")
4522  PTR#DAT%=18
4525  next%=11
4530 REPEAT
4535  INPUT#DAT%,date$,in%,end%
4536 REPEAT
```

```
4540  PTR#ATT%=next%+23
4542  d$="":
4543 FOR Y%=1 TO 3
4544 p$=STR$BGET#ATT%:IF LENp$=1 THEN p$="0"+p$
4545  d$=d$+p$
4546 NEXT
4547  PRINTdate$,d$
4599 CLOSE#0
4600 STOP
4630 DEFPROC_BLANK(P%)
4640  NAME$(P%)="
":UNIT$(P%)="000000":LMP$(P%)="00/00/00":EDD$(P%)="00/00/00"
:GEST$(P%)="0+0"
4642  CON$(P%)="0":REFERAL$(P%,0)="00/00/00":REFERAL$(P%,1)="0"
:REFERAL$(P%,2)="0"
4650  RESULTS$(P%,0)="0.0":RESULTS$(P%,1)="000"
:RESULTS$(P%,2)="00.0":RESULTS$(P%,3)="000"
:RESULTS$(P%,4)="0":CTGAN$(P%)="0"
4652   FUAN$(P%,0)="0":FUAN$(P%,1)="0":FUAN$(P%,2)="00/00/00"
4660  DIAGAN$(P%)="0":REFDATE$(P%)="00/00/00"
:REFBP$(P%)="000/000":FORX%=0  TO  6:DCBP$(P%,X%)="000/000":NEXT
:BKBP$(P%)="000/000"
4662   BKGEST$(P%)="0":BP28$(P%)="000/000":PARITY$(P%)="0+0"\
:ATTNO$(P%)="0":DOB$(P%)="00/00/00"
4670   FHR$(P%)="000"
4680 ENDPROC
4682 DEFPROC_CLEARCURRENT
4683 LOCAL P%
4684 FORP%=0 TO 8:PROC_BLANK(P%):NEXT
4690   TDDATE$="00/00/00"
4700 ENDPROC
4705  :
4710 DEFPROC_BPUT
4720  FORX%=1 TO 15:BPUT#ATT%,ASCMID$(NAME$(P%),X%,1):NEXT
4730  FORX%=1 TO 5 STEP2:BPUT#ATT%,VALMID$(UNIT$(P%),X%,2):NEXT
4740  FORX%=1 TO 7 STEP3:BPUT#ATT%,VALMID$(DOB$(P%),X%,2):NEXT
4750  FORX%=1 TO 3 STEP2:BPUT#ATT%,VALMID$(PARITY$(P%),X%,1):NEXT
4760 FORX%=1 TO 7 STEP3:BPUT#ATT%,VALMID$(TDDATE$,X%,2):NEXT
4770  BPUT#ATT%,VALATTNO$(P%)
4780  FORX%=1 TO 7 STEP3:BPUT#ATT%,VALMID$(LMP$(P%),X%,2):NEXT
4790  FORX%=1 TO 7 STEP3:BPUT#ATT%,VALMID$(EDD$(P%),X%,2):NEXT
4800  BPUT#ATT%,VALGEST$(P%)
4810  FORX%=1 TO 7 STEP3:BPUT#ATT%,VALMID$(REFDATE$(P%),X%,2):NEXT
4820  FORX%=1 TO 5 STEP 4:BPUT#ATT%,VALMID$(REFBP$(P%),X%,3):NEXT
4830  FORX%=1 TO 5 STEP 4:BPUT#ATT%,VALMID$(BKBP$(P%),X%,3):NEXT
4840  BPUT#ATT%,VALBKGEST$(P%)
4850  FORX%=1 TO 5 STEP 4:BPUT#ATT%,VALMID$(BP28$(P%),X%,3):NEXT
4860  BPUT#ATT%,VALCON$(P%)
5010  BPUT#ATT%,VALREFERAL$(P%,1)
5020  BPUT#ATT%,VALREFERAL$(P%,2)
5030 FORY%=0 TO 6
5040 FORX%=1 TO 5 STEP 4
:BPUT#ATT%,VALMID$(DCBP$(P%,Y%),X%,3):NEXT
5050 NEXT
5060   BPUT#ATT%,(VAL(RESULTS$(P%,0))*10)
5070   BPUT#ATT%,(VALRESULTS$(P%,1)/3)
5080   BPUT#ATT%,(VAL(RESULTS$(P%,2))*10)
```

```
 5090  BPUT#ATT%,(VALRESULTS$(P%,3)/2)
 5100  BPUT#ATT%,VALRESULTS$(P%,4)
 5110  BPUT#ATT%,VALCTGAN$(P%)
 5120  BPUT#ATT%,VAL(FHR$(P%))
 5130  BPUT#ATT%,VALFUAN$(P%,1)
 5140 FORX%=1 TO 7 STEP 3:BPUT#ATT%,VALMID$(FUAN$(P%,2),X%,2):NEXT
:BPUT#ATT%,VALDIAGAN$(P%)
 5150 ENDPROC
 5160  :
 5170 DEFPROC_PRINT
 5180  CLS:IF  TDDATE$="00/00/00"  THEN
PROC_DH(2,4,CHR$129+"THERE IS NO DATA ON FILE"):PROC_SPACE:ENDPROC
 5190 PROC_DH(2,4,CHR$129+"PRINTING RECORDS FOR "+TDDATE$)
 5210 PROC_DH(5,8,CHR$131+"DO YOU WISH TO CONTINUE ?")
:AN$=FN_ANSWER("YN"):IF AN$="N"THEN ENDPROC
 5240 FOR P%=0 TO 8:PROC_CASE:NEXT
 5270 CLS:PROC_DH(5,8,CHR$131+"REPEAT PROCESS ?")
 5280  AN$=FN_ANSWER("YN")
 5290 IF AN$="Y"THEN GOTO5180 ELSE ENDPROC
 5300 DEFPROC_CASE
 5310  VDU15
 5320 IF LEFT$(NAME$(P%),5)="     " THEN ENDPROC
 5330  CLS:PROC_DH(8,10,""+NAME$(P%))
 5340 PROC_DH(8,14,"DO YOU WISH TO PRINT"):A$=GET$
 5345 IF A$="N" ENDPROC
 5346 IF VALATTNO$(P%)>1 THEN CLS:PROC_DH(0,4,"FOR "+NAME$(P%))
:PROC_DH(0,8,"FIRST ATTENDANCE DATE 00/00/00 ")
:first$=FN_DATE(13,11,84,86)
 5350 MODE 0
 5360  VDU2
 5370  PRINT"VISIT ";ATTNO$(P%);TAB(50);"Consultant - "
;CONS$(VAL(CON$(P%))):PRINT
 5380  PRINT"Name  - ";NAME$(P%);TAB(30);"Para  ";PARITY$(P%);TAB(40)
;"Gestation ";GEST$(P%);TAB(60);"Date ";TDDATE$
 5390  PRINT'"Unit  No. ";UNIT$(P%);TAB(20);"DOB  ";DOB$(P%);TAB(40)
;"LMP  ";LMP$(P%);TAB(60);"EDD  ";EDD$(P%)
 5400 PRINT'"This patient was refered from the
";REF1$(VAL(REFERAL$(P%,1)));" on  "
;REFDATE$(P%)
 5410  PRINT"Reason for referal was ";REF2$(VAL(REFERAL$(P%,2)))
;". Blood pressure was ";REFBP$(P%)
 5420 LATER%=FN_LATER(REFDATE$(P%),TDDATE$)
 5430 PROC_ANCSUM
 5440 PRINT'"The patient was seen at Day Care on ";TDDATE$;" "
;LATER%;" days after referal"
 5445 IF VALATTNO$(P%)>1 THEN PRINT'"Previous attendances : "
:extra%=1:PROC_PATIENT:extra%=0:PRINT'"Todays attendance :-"
 5450 PRINT:FORX%=0 TO 3:PRINTTAB(5);X%+1;") Blood Pressure - "
;DCBP$(P%,X%);TAB(40);TEST$(X%);TAB(60);"-  ";RESULTS$(P%,X%):NEXT
 5460  PRINTTAB(5);5") Blood Pressure - "
;DCBP$(P%,4);TAB(40);TEST$(4);TAB(60);"-   "
;PROT$(VAL(RESULTS$(P%,4)))
 5470 PROC_AVERAGEBP
 5480 PRINT"Average Blood Pressure - "
;DCBP$(P%,6);TAB(40);"Cardiotocograph";TAB(60);"-   "
;CTG$(VAL(CTGAN$(P%)))
 5490  PRINT"Dinamap Blood Pressure  - ";DCBP$(P%,5);TAB(40)
```

```
;"Fetal Heart Rate ";TAB(60);"- ";FHR$(P%)
 5500 PRINT"The diagnosis at Day Assessment was "DIAG$(VAL(DIAGAN$(P%)))
 5510  FU%=FN_LATER(TDDATE$,FUAN$(P%,2))
 5520  PRINT"Follow up will be at ";FU$(VAL(FUAN$(P%,1)));" on "
;FUAN$(P%,2)"' ( ";FU%;" days after the Day Care attendance)"
 5530 MODE 7
 5540  VDU3
 5550 GOTO5330
 5560  :
 5570 DEFPROC_ANCSUM
 5580  PRINT"'Blood pressure at ";BKGEST$(P%);" weeks was ";BKBP$(P%)
 5590  PRINT"Blood pressure at 28-30 weeks was ";BP28$(P%)
 5600 ENDPROC
 5640  :
 5650 DEFPROC_LIST
 5660 PROC_LISTMENU
 5670 IFANS$="1"THENPROC_ALL
 5680 IFANS$="2"THENPROC_BIRTH
 5690 IFANS$="3"THENCHAIN"WEEKRVU"
 5700 IFANS$="4"THEN CHAIN"FILCHEK"
 5710  IFANS$="5"THEN
 5720 IFANS$="E"THEN CLS:ENDPROC
 5725  GOTO5660
 5730 DEFPROC_LISTMENU
 5740 MODE 7:ADD$="PROGRAM":CLOSE#0:HEAD$="LISTING":PROC_HEAD
 5750  PROC_DH(5,2,CHR$129+"1) LIST ALL PATIENTS")
 5760 PROC_DH(5,4,CHR$129+"2) LIST ALL DELIVERED PATIENTS")
 5770  PROC_DH(5,6,CHR$129+"3) WEEKLY REVIEW")
 5780  PROC_DH(5,8,CHR$129+"4) LIST ALL DATES")
 5790  PROC_DH(5,10,CHR$129+"5) LIST SELECTED PATIENTS")
 5799  ANS$=FN_ANSWER("12345")
 5800 ENDPROC
 5810  :
 6000 DEFPROC_AXESFIL
 6010 axes%=1:PROC_CLEARCURRENT
 6030 PROC_AXMENU
 6040 IFANS$="1"THENPROC_PATIENT
 6050 IFANS$="2"THENPROC_ACCESSDAY
 6060  IFANS$="3"THENPROC_PRINT
 6070  IFANS$="4"THENCHAIN"DINARED"
 6075 IFANS$="5"THENCHAIN"WEEKRVU"
 6077 IFANS$="6"THENCHAIN"SPACECK"
 6120 IFANS$="E"THENCLS:PROC_INFO:ENDPROC
 6130  GOTO6030
 6140  :
 6150 DEFPROC_AXMENU
 6155 MODE 7:ADD$="PROGRAM":CLOSE#0:HEAD$="ACCESS":PROC_HEAD
 6160  PROC_DH(5,2,CHR$129+"1)  FIND  PATIENT")
 6170  PROC_DH(5,4,CHR$129+"2)  FIND  DATE")
 6180  PROC_DH(5,6,CHR$129+"3)  PRINT CURRENT FILE")
 6220  PROC_DH(5,8,CHR$129+"4)  READ DINADATA")
 6230  PROC_DH(5,10,CHR$129+"5)  WEEKLY REVUE")
 6235  PROC_DH(5,12,CHR$129+"6)  SPACE CHECK")
 6240  ANS$=FN_ANSWER("123456")
 6250 ENDPROC
 6260  :
 6270 DEFPROC_ACCESSDAY
```

```
6280 ADD$="DATE ACCESS":PROC_HEAD
6290  PROC_DH(0,8,"WHICH  DATE  00/00/00  ")
:TDDATE$=FN_DATE(13,11,84,86)
6300  FILE$=LEFT$(TDDATE$,2)+MID$(TDDATE$,4,2)+RIGHT$(TDDATE$,2)
6310  PROC_FINDDATE(FILE$,1)
6320 IF date%>0 ORdate%<0 THENPROC_DH(0,15,"DATE NOT ON FILE "):VDU7
:PROC_DH(0,17," INPUT ANOTHER DATE ?"):Y$=GET$ ELSE GOTO 6330
6325 IF Y$="Y" THEN CLS:GOTO 6290 ELSE ENDPROC
6330  INPUT#DAT%,begin%,end%:CLOSE#DAT%
6335 IF ram%=0 THEN dr%=2 ELSE dr%=5
6340  PROC_OPEN(FILE$,2,dr%)
6350  P%=0
6360 FOR patient%=begin% TO end% STEP 80
6370  address%(P%)=patient%
6380  NAME$(P%)=""
6390 PROC_BGET
6410  P%=P%+1
6420  PAT%=P%
6430 NEXT
6440 CLOSE#ATT%
6450  gotit%=-1:PROC_DISPLAY
6460 ENDPROC
6470  :
6480 DEFPROC_PATIENT
6485 IF extra%=1 THEN NAME$=NAME$(P%):last$=TDDATE$:GOTO6510
6490 CLS:ADD$="PATIENT SEARCH":PROC_HEAD
6500 PRINTTAB(3,3)"DO YOU KNOW THE ATTENDANCE DATE ?":Y$=GET$
:IF Y$="Y"THEN PROC_ACCESSDAY:ENDPROC
6505 CLS
6510 PROC_SELECT:start%=begin%
6512  bit%=0:att%=0
6515 IF extra%=1 THEN GOTO6570
6520  PRINTTAB(0,2);"NAME  (A  SMITH)"
6540 CLS:PRINTTAB(0,2)"INPUT NAME  (A SMITH)"
6550  NAME$=FN_NAMEINPUT(20,2)
6560 IFLEFT$(NAME$,2)="  "THEN NAME$=RIGHT$(NAME$,LENNAME$-2)
6570*  FX15,1
6580  YEAR$="0008"+RIGHT$(first$,2)
6590 PROC_OPEN(YEAR$,2,5)
6600  INPUT#ATT%,finish%
6610 IF extra%=1  THEN print$="Y":GOTO6615
6611 CLS:PROC_DH(5,5,CHR$129+"PATIENT ATTENDANCE SUMMARY")
6612 PROC_DH(5,7,CHR$129+"DO YOU WISH TO PRINT SUMMARY?")
6613  print$=GET$
6615  temp%=P%
6620 REPEAT
6630  gotit%=0:again%=0:P%=9
6640  NAME$(P%)="":address%(P%)=start%:PTR#ATT%=address%(P%)
6650 FORX%=1  TO  15:NAME$(P%)=NAME$(P%)+CHR$(BGET#ATT%):NEXT
6660  gotit%=INSTR(NAME$(P%),NAME$)
6665 IF gotit%>0 THEN NAME$(P%)="":PROC_BGET:PROC_PATSUM
6670  start%=start%+80
6680 UNTIL start%>=end% OR start%>=finish%
6685 CLOSE#0
6690 IF extra%=1 THEN P%=temp%:ENDPROC
6692 VDU3
6710 PROC_SPACE
```

```
6711 MODE 7
6712 PROC_DH(0,5,"ÅANOTHER PATIENT ?")
6713 CLOSE#0
6715  P%=temp%
6720 ENDPROC
6730  :
6740 DEFPROC_ALL
6750 CLS:PROC_SELECT
6755  page%=0:number%=0
6760  patient%=begin%
6770 PRINT'"PRINTER Y/N?":Y$=GET$
6775 PRINT'"FIRST VISITS ONLY ?":fst$=GET$
6780  MODE 3:PROC_OPEN("0008"+YR$,2)
6790 IFY$="Y" THEN VDU2
6800 PRINTTAB(18)"ALL ATTENDANCES BETWEEN ";first$;" AND ";last$
6810  REPEAT:P%=0:number%=number%+1
6820  NAME$(P%)="":address%(P%)=patient%:PROC_BGET
6830 IF page% MOD 55=0 AND page%>0  THEN VDU3,7:PROC_SPACE
:IF Y$="Y"THENVDU2
6835 IF fst$="Y" AND VAL(ATTNO$(P%))>1 THEN GOTO6850
6840  page%=page%+1:PRINTnumber%;")  "
;NAME$(P%),UNIT$(P%),ATTDATE$(P%),"Visit  "
;ATTNO$(P%),"at ";GEST$(P%);" weeks"
6850  patient%=patient%+80
6860 UNTILPTR#ATT%>end%
6870 CLOSE#ATT%:VDU3:PROC_SPACE:MODE 7:ENDPROC
6880  :
6890 DEFPROC_SAVE
6895 FOR dr%=2 TO 5 STEP 3
6900  PROC_OPEN("000888",2,dr%)
6905  PTR#ATT%=address%(P%)
6910 PROC_BPUT
6920 CLOSE#ATT%
6925 NEXT
6930 ENDPROC
6940  :
7040 DEFPROC_SELECT
7045 IF extra%=1 THEN VDU3:GOTO 7062
7050  PRINTTAB(0,2)"FIRST  DAY  00/00/00":DATE$=FN_DATE(20,2,84,86)
:first$=LEFT$(DATE$,2)+MID$(DATE$,4,2)+RIGHT$(DATE$,2)
7052  YR$=RIGHT$(first$,2)
7060  PRINTTAB(0,4)"LAST   DAY  00/00/00":DATE$=FN_DATE(20,4,84,86)
:last$=LEFT$(DATE$,2)+MID$(DATE$,4,2)+RIGHT$(DATE$,2)
7062  YR$=RIGHT$(first$,2)
7070  PROC_FINDDATE(first$,1)
7080  SP%=SP%-DATlength%
7090 IFSP%=0 THEN SP%=18
7100  PTR#DAT%=SP%:INPUT#DAT%,DUMMY1$,begin%
7110 CLOSE#DAT%
7120  PROC_FINDDATE(last$,SP%/DATlength%)
7130  SP%=SP%-DATlength%
7140  PTR#DAT%=SP%:INPUT#DAT%,DUMMY1$,dummy%,end%
7145 IF extra%=1 THEN VDU2
7147 CLOSE#DAT%:ENDPROC
7150  :
7160 DEFPROC_BYTESELECT(byte%,expression$,end%)
7170 REPEAT
```

```
 7180  match%=0
 7190  PTR#ATT%=SP%+byte%
 7200 BYTE%=BGET#ATT%
 7210  IF  EVAL(expression$)THENmatch%=1:SP%=SP%-80
 7220  SP%=SP%+80
 7230 UNTIL SP%=end% OR match%=1
 7240 ENDPROC
 7250  :
 7260 DEFFN_DATESELECT(byte%)
 7270  PTR#ATT%=SP%+byte%
 7280  =FN_BACK(3,2,"/")
 7290  :
 7300 DEFPROC_FINDDATE(dt$,st%)
 7310  PROC_OPEN(dt$,1,ram%)
 7320  INPUT#DAT%,DATinput%,DATlength%
 7330  SP%=DATlength%
 7340 REPEAT
 7350  PTR#DAT%=SP%:INPUT#DAT%,DAT$:date%=FN_LATER(dt$,DAT$)
 7351 IF DAT$="000000" THEN SP%=SP%+DATlength%:GOTO 7370
 7352 PRINTTAB(2,15)CHR$141CHR$129"SEARCH DATE ";DAT$
:PRINTTAB(2,16)CHR$141CHR$129"SEARCH DATE ";DAT$
 7353 IF date%>-5 THEN SP%=SP%+DATlength%:GOTO 7370
 7355 IF date%<0 THEN SP%=SP%+(DATlength%*INT(ABSdate%/4))
 7370 UNTILdate%>=0 OR SP%>=DATinput%
 7380 ENDPROC
 7390  :
 7400  DEFPROC_OPEN(dt$,W%,dr%)
 7410 IF dr%=5 AND ram%=0 THEN dr%=2
 7420 IF dr%=4 AND ram%=0 THEN dr%=0
 7430 IF W%=1 THEN DAT%=OPENIN(":"+STR$dr%+".DTINX88") ELSE
ATT%=OPENUP(":"+STR$dr%+".DC/FL88")
 7470 ENDPROC
 7480  :
 7490 DEFPROC_BIRTH
 7495 CLS:PROC_SELECT:SP%=begin%
 7500 PRINT'"PRINTER Y/N":Y$=GET$
 7510 PRINT'"FIRST ATTENDANCE ONLY Y/N":att$=GET$:MODE 3
 7520 IF Y$="Y"THENVDU2
 7530  PROC_OPEN("000086",2,5)
 7550  P%=0
 7560 REPEAT
 7570 date$=FN_DATESELECT(27)
 7580 IF att$="Y" THEN PROC_BYTESELECT(26,"BYTE%=1",end%) ELSE
match%=1
 7590 date%=VALFN_GEST(date$,TDDATE$)
 7600 IF date%>44 AND match%=1 THEN
address%(P%)=SP%:PROC_BGET:PRINTSTR$((SP%-11)/80+1);")  "
;NAME$(P%),UNIT$(P%),"Attended  ";
 7602 PRINTATTDATE$(P%),"EDD was ";EDD$(P%)
 7610  SP%=SP%+80
 7620 UNTIL SP%=end%
 7630 CLOSE#ATT%:VDU3:ENDPROC
 7640  :
 7650 DEFPROC_BGET
 7660  PTR#ATT%=address%(P%)
 7670  NAME$(P%)="":FORX%=1 TO 15
:NAME$(P%)=NAME$(P%)+CHR$(BGET#ATT%):NEXT
```

```
7680  UNIT$(P%)=FN_BACK(3,2,"")
7690  DOB$(P%)=FN_BACK(3,2,"/")
7700  PARITY$(P%)=FN_BACK(2,1,"+")
7710  ATTDATE$(P%)=FN_BACK(3,2,"/")
7720 ATTNO$(P%)=STR$(BGET#ATT%)
7730  LMP$(P%)=FN_BACK(3,2,"/")
7740  EDD$(P%)=FN_BACK(3,2,"/")
7750 GEST$(P%)=STR$(BGET#ATT%)
7760  REFDATE$(P%)=FN_BACK(3,2,"/")
7770  REFBP$(P%)=FN_BACK(2,3,"/")
7780  BKBP$(P%)=FN_BACK(2,3,"/")
7790 BKGEST$(P%)=STR$(BGET#ATT%)
7800  BP28$(P%)=FN_BACK(2,3,"/")
7810 CON$(P%)=STR$(BGET#ATT%)
7820 IFVALCON$(P%)>7 THEN CON$(P%)="0"
7830  REFERAL$(P%,1)=STR$(BGET#ATT%)
7840 IFVALREFERAL$(P%,1)>3 THENREFERAL$(P%,1)="0"
7850  REFERAL$(P%,2)=STR$(BGET#ATT%)
7860 IFVALREFERAL$(P%,2)>5 THENREFERAL$(P%,2)="0"
7870 FORY%=0 TO 6:DCBP$(P%,Y%)=FN_BACK(2,3,"/"):NEXT
7880  RESULTS$(P%,0)=STR$(BGET#ATT%/10)
7890  RESULTS$(P%,1)=STR$(BGET#ATT%*3)
7900  RESULTS$(P%,2)=STR$(BGET#ATT%/10)
7910  RESULTS$(P%,3)=STR$(BGET#ATT%*2)
7920  RESULTS$(P%,4)=STR$(BGET#ATT%)
7930 IFVALRESULTS$(P%,4)>5 THEN RESULTS$(P%,4)="0"
7940 CTGAN$(P%)=STR$(BGET#ATT%)
7950 IFVALCTGAN$(P%)>3 THENCTGAN$(P%)="0"
7960  FHR$(P%)=STR$(BGET#ATT%)
7970  FUAN$(P%,1)=STR$(BGET#ATT%)
7980  IFVALFUAN$(P%,1)>3  THENFUAN$(P%,1)="0"
7990  FUAN$(P%,2)=FN_BACK(3,2,"/")
8000  DIAGAN$(P%)=STR$(BGET#ATT%)
8010 IFVALDIAGAN$(P%)>4 THENDIAGAN$(P%)="0"
8020 ENDPROC
8030  :
8040  DEFFN_BACK(x%,n%,slash$)
8050  LOCALX%:tot$=""
8060 FORX%=1 TO x%
8070  t$=STR$(BGET#ATT%)
8080 IFLENt$<n% THEN t$="0"+t$:GOTO8080
8090  tot$=tot$+t$:IFX%<x% THEN tot$=tot$+slash$
8100 NEXT
8110  =tot$
8120  :
8130  UNIT$(P%)=FN_BACK(3,2,"")
8140  DOB$(P%)=FN_BACK(3,2,"/")
8150  PARITY$(P%)=FN_BACK(2,1,"+")
8160  ATTDATE$(P%)=FN_BACK(3,2,"/")
8170 ATTNO$(P%)=STR$(BGET#ATT%)
8180  LMP$(P%)=FN_BACK(3,2,"/")
8190  EDD$(P%)=FN_BACK(3,2,"/")
8200  GEST$(P%)=STR$(BGET#ATT%)
8210  REFDATE$(P%)=FN_BACK(3,2,"/")
8220  REFBP$(P%)=FN_BACK(2,3,"/")
8230  BKBP$(P%)=FN_BACK(2,3,"/")
8240  BKGEST$(P%)=STR$(BGET#ATT%)
```

```
8250  BP28$(P%)=FN_BACK(2,3,"/")
8260 CON$(P%)=STR$(BGET#ATT%)
8270 IFVALCON$(P%)>7 THEN CON$(P%)="0"
8280  REFERAL$(P%,1)=STR$(BGET#ATT%)
8290 IFVALREFERAL$(P%,1)>3 THENREFERAL$(P%,1)="0"
8300  REFERAL$(P%,2)=STR$(BGET#ATT%)
8310 IFVALREFERAL$(P%,2)>5 THENREFERAL$(P%,2)="0"
8320 FORY%=0 TO 6:DCBP$(P%,Y%)=FN_BACK(2,3,"/"):NEXT
8330  RESULTS$(P%,0)=STR$(BGET#ATT%/10)
8340  RESULTS$(P%,1)=STR$(BGET#ATT%*3)
8350  RESULTS$(P%,2)=STR$(BGET#ATT%/10)
8360  RESULTS$(P%,3)=STR$(BGET#ATT%*2)
8370  RESULTS$(P%,4)=STR$(BGET#ATT%)
8380 IFVALRESULTS$(P%,4)>5 THEN RESULTS$(P%,4)="0"
8390 CTGAN$(P%)=STR$(BGET#ATT%)
8400 IFVALCTGAN$(P%)>3 THENCTGAN$(P%)="0"
8410  FHR$(P%)=STR$(BGET#ATT%)
8420  FUAN$(P%,1)=STR$(BGET#ATT%)
8430  IFVALFUAN$(P%,1)>3  THENFUAN$(P%,1)="0"
8440  FUAN$(P%,2)=FN_BACK(3,2,"/")
8450 DIAGAN$(P%)=STR$(BGET#ATT%)
8460 IFVALDIAGAN$(P%)>4 THENDIAGAN$(P%)="0"
8470 ENDPROC
8500  DEFFN_BACK(x%,n%,slash$)
8510 LOCALX%:tot$=""
8520 FORX%=1 TO x%
8530  t$=STR$(BGET#ATT%)
8540 IFLENt$<n% THEN t$="0"+t$:GOTO8540
8550  tot$=tot$+t$:IFX%<x% THEN  tot$=tot$+slash$
8560 NEXT
8570  =tot$
9000 DEFPROC_PATSUM
9001 IF att%>0 THEN GOTO 9045
9002 IF extra%=1 THEN VDU2:GOTO9040
9010  MODE  3:VDU19,1,6,0,0,0
9015 IF print$="Y" THEN VDU2
9016 PRINTTAB(20)"PATIENT ATTENDANCE SUMMARY"
9017  PRINT
9020  PRINTNAME$(P%);TAB(16);"PARA ";PARITY$(P%);TAB(28);"UNIT  NO "
;UNIT$(P%);TAB(45);"DOB  ";DOB$(P%);TAB(60);"LMP  ";LMP$(P%)
9025  PRINT
9030 PRINT"BOOKING BP AT "BKGEST$(P%);"wk BP was ";BKBP$(P%)
;" and at 28wk BP ";BP28$(P%)
9035 PRINT'"CONSULTANT ";CONS$(VALCON$(P%))
9040  PRINT'"   DATE";TAB(9)"Gest";TAB(13)"  Av  BP";TAB(22);"Urea";TAB(27)
;"Uric";TAB(32);"Haem";TAB(37)"Plat";TAB(42)"  CTG";TAB(52)"FHR"
;TAB(57)"Diagnosis":att%=2
9045 IF print$="Y" THEN VDU2
9050  PRINTATTDATE$(P%);TAB(10)GEST$(P%);TAB(13)DCBP$(P%,6)
;TAB(22)RESULTS$(P%,0);TAB(27);RESULTS$(P%,1);TAB(32)
;RESULTS$(P%,2);TAB(37)RESULTS$(P%,3);TAB(42)CTG$(VALCTGAN$(P%))
;TAB(52)FHR$(P%);TAB(57)LEFT$(DIAG$(VAL(DIAGAN$(P%))),9)
9060 ENDPROC
10000 DEFPROC_RESULTS
10010 M%=0:IF axes%=1 THEN TDDATE$=ATTDATE$(P%)
10020 ADD$="RESULTS":HEAD$="DAYCARE (1988)":PROC_HEAD
10030  PROC_DH(0,0,STR$(P%+1)+" "+CHR$131+NAME$(P%)+"          "
```

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+UNIT$(P%))
10040 PROC_DH(5,3,CHR$129+"1) BASIC DATA")
10050 PROC_DH(5,5,CHR$129+"2) BLOOD PRESSURES")
10060 PROC_DH(5,7,CHR$129+"3) BIOCHEMISTRY/HAEMOTOLOGY")
10070 PROC_DH(5,9,CHR$129+"4) URINALYSIS")
10080 PROC_DH(5,11,CHR$129+"5) CARDIOTOCOGRAPH")
10090 PROC_DH(5,13,CHR$129+"6) FOLLOWUP/DIAGNOSIS")
10100 PROC_DH(5,15,CHR$129+"7) FULL DISPLAY")
10110 IF axes%<>0 PROC_DH(5,17,CHR$129+"8) PRINT INFORMATION")
10115* FX15,1
10120 AN$=FN_ANSWER("12345678")
10130 IFAN$="1"THENPROC_BASICDATA
10140 IFAN$="2"THENM%=1:PROC_DCBP
10150 IFAN$="3"THENM%=1:PROC_BIOCHEM
10160 IFAN$="4"THENM%=1:PROC_PROT
10170 IFAN$="5"THENM%=1:PROC_CTG
10180 IFAN$="6"THENM%=1:PROC_FUDIAG
10190 IFAN$="7"THENPROC_DISPLAY1:PROC_DISPLAY2
10205 IFAN$="8" AND axes%=1 THENPROC_CASE
10210 IFAN$="E"THENAN$="":ENDPROC
10230 GOTO10020
10240 :
10250 DEFPROC_DISPLAY
10260 IFPAT%=0 THEN PROC_BASICDATA
10270 ADD$=TDDATE$:HEAD$="DAYCARE":PROC_HEAD
10280 M%=0
10290 FORP%=0 TO PAT%-1
10300 IF NAME$(P%)="              " OR NAME$(P%)="" THEN
PAT%=P%:P%=8:GOTO10320
10310 IF gotit%>0 AND axes%=1 THEN
PROC_DH(0,P%*2,STR$(P%+1)+CHR$133+NAME$(P%)+"  "+UNIT$(P%)+"  "
+ATTDATE$(P%))
ELSEPROC_DH(0,P%*2,STR$(P%+1)+CHR$133+NAME$(P%)+"          "
+UNIT$(P%))
10320 NEXT
10330 IFPAT%=9 THEN pat%=PAT%-1:GOTO10350 ELSE pat%=PAT%
10340 IF gotit%>0 AND axes%=1 THEN
PROC_DH(0,P%*2,STR$(P%+1)+CHR$129+"NEXT SAMPLE FOR SAME PAIENT")
10350 IF gotit%=0 AND axes%=1 THEN PROC_DH(2,P%*2,CHR$131+"NO MORE
SAMPLES FOR THIS PATIENT")
10351 IF axes%=0 THENPROC_DH(0,PAT%*2+1,STR$(PAT%+1)+CHR$129
+"ADD ANOTHER PATIENT")
10360 IF gotit%=0 AND axes%=1 THEN
P$=FN_ANSWER(LEFT$("123456789",pat%)) ELSE
P$=FN_ANSWER(LEFT$("123456789",pat%+1))
10370 IFP$="E"THENCLS:ENDPROC
10375 IFP$="S"THENPROC_SPECIAL
10380 P%=VAL(P$)-1
10390 IFP%=PAT% AND axes%=1 THEN again%=1:ENDPROC
10395 IFP%=PAT% AND axes%=0 THEN
PAT%=PAT%+1:PROC_BASICDATA:GOTO10270
10400 PROC_RESULTS
10410 IFM%=1 AND axes%=0 THENM%=0:PROC_SAVECURRENT
10415 IFM%=1AND axes%=1 THENM%=0:PROC_SAVE
10420 GOTO10270
10430 :
10440 DEFPROC_BIOCHEM
```

```
10450 CLS:PROC_DH(0,1,STR$(P%+1)+CHR$129+NAME$(P%)+"          "
+UNIT$(P%))
10460 FORT%=0 TO 3:PRINTTAB(0,4+(T%*2));T%+1;")"+CHR$129
;TEST$(T%);TAB(20);CHR$131;RESULTS$(P%,T%):NEXT
10470 AN$=FN_ANSWER("1234"):an%=VALAN$-1
10480 IFAN$="E"THENAN$="":ENDPROC
10490
RESULTS$(P%,an%)=FN_INPUT(21,4+(an%*2),4,num$+"."):GOTO10470
10500 :
10510 DEFPROC_DISPLAY1
10520 CLS:VDU28,0,24,39,3:PRINTTAB(0,1)NAME$(P%);TAB(16,1);"PARA "
;PARITY$(P%);TAB(28,1);"GESTÉ";GEST$(P%)
10530 PRINTTAB(0,2);"UNIT NO "
;UNIT$(P%);TAB(16,2);"DOB";DOB$(P%);TAB(28,2);"LMP";LMP$(P%)
10540 VDU28,0,24,39,6
10550 ENDPROC
10560 :
10570 DEFPROC_DCBP
10580 CLS:PROC_DH(0,1,STR$(P%+1)+CHR$129+NAME$(P%)+"
"+UNIT$(P%))
10590 FORT%=0 TO 4:PRINTTAB(0,4+(T%*2));T%+1;") Blood Pressure :"
;CHR$131;TAB(20);DCBP$(P%,T%):NEXT
10600 PRINTTAB(0,14)"Av Blood Pressure :";CHR$129;TAB(20);DCBP$(P%,6)
10610 AN$=FN_ANSWER("12345")
10620 IFAN$="E"THENAN$="":ENDPROC
10630 DCBP$(P%,VAL(AN$)-1)=FN_BP(20,4+((VAL(AN$)-1)*2))
10640 PROC_AVERAGEBP
10650 PRINTTAB(20,14);DCBP$(P%,6):GOTO10610
10660 :
10670 DEFPROC_AVERAGEBP
10680 SYST%=0:DIAST%=0:NUM%=0
10690 FORX%=0 TO 4
10700 IF VALDCBP$(P%,X%)=0 THEN 10720
10710 SYST%=SYST%+VAL(LEFT$(DCBP$(P%,X%),3))
:DIAST%=DIAST%+VAL(RIGHT$(DCBP$(P%,X%),3)):NUM%=NUM%+1
10720 NEXT
10730 IFNUM%=0 THEN DCBP$(P%,6)="000/000":ENDPROC
10740 SYST%=SYST%/NUM%:SYST$=STR$(SYST%)
:DIAST%=DIAST%/NUM%:DIAST$=STR$(DIAST%)
10750 IFLENSYST$<3 THEN SYST$="0"+SYST$:GOTO10750
10760 IFLENDIAST$<3 THEN DIAST$="0"+DIAST$:GOTO10760
10770 DCBP$(P%,6)=SYST$+"/"+DIAST$
10780 ENDPROC
10790 :
10800 DEFPROC_PROT
10810 CLS:PROC_DH(0,1,STR$(P%+1)+CHR$129+NAME$(P%)+"          "
+UNIT$(P%))
10820 PRINTTAB(5,4);CHR$132;"URINALYSIS WARD TESTING"
10830 FORT%=0 TO 5:PRINTTAB(10,5+(T%*2));T%+1;") ";PROT$(T%):NEXT
10840 PRINTTAB(20,5+(VAL(RESULTS$(P%,4))));"Å<==";
:GOTOFN_OK(10850,10900)
10850 PRINTTAB(20,5+(VAL(RESULTS$(P%,4))));"       "
10860 AN$=FN_ANSWER("12345")
10870 IFAN$="E"THENAN$="":ENDPROC ELSE an%=VALAN$-1
10880 PRINTTAB(20,5+(an%*2));"Å<==";:GOTOFN_OK(10820,10890)
10890 RESULTS$(P%,4)=STR$(an%)
10900 ENDPROC
```

```
10910 :
10920 DEFPROC_CTG
10930 CLS:PROC_DH(0,1,STR$(P%+1)+CHR$129+NAME$(P%)+"          "
+UNIT$(P%))
10940 PRINTTAB(1,4);"CARDIOTOCOGRAPH RESULTS"
10950 FORT%=0 TO 3:PRINTTAB(0,5+(T%*2));T%+1;") ";CTG$(T%):NEXT
10960 PRINTTAB(20,5+(VAL(CTGAN$(P%))));"Å<==";
:GOTOFN_OK(10970,11030)
10970 PRINTTAB(20,5+(VAL(CTGAN$(P%))));"          "
10980 AN$=FN_ANSWER("1234")
10990 IFAN$="E"THENAN$="":ENDPROC ELSE an%=VALAN$-1
11000 PRINTTAB(20,5+(an%*2));"Å<==";:GOTOFN_OK(10940,11010)
11010 CTGAN$(P%)=STR$(an%)
11020 PRINTTAB(5,15);"ÇBASAL FETAL HEART RATEá"
:FHR$(P%)=FN_INPUT(30,15,3,num$):GOTOFN_OK(11020,11030)
11030 ENDPROC
11040 :
11050 DEFPROC_FUDIAG
11060 CLS:PROC_DH(0,1,STR$(P%+1)+CHR$129+NAME$(P%)+"          "
+UNIT$(P%))
11070 PRINTTAB(5,4);"DIAGNOSIS"
11080 FORT%=0 TO 4:PRINTTAB(0,6+(T%*2));T%+1;") ";DIAG$(T%):NEXT
11090 PRINTTAB(30,6+(VAL(DIAGAN$(P%))*2));"Å<==";
:GOTOFN_OK(11110,11150)
11100 PRINTTAB(30,6+(VAL(DIAGAN$(P%))*2));"          "
11110 AN$=FN_ANSWER("12345")
11120 IFAN$="E"THENAN$="":GOTO4540 ELSE an%=VALAN$-1
11130 PRINTTAB(30,6+(an%*2));"Å<==";:GOTOFN_OK(11070,11140)
11140 DIAGAN$(P%)=STR$(an%)
11150 CLS:PROC_DH(0,1,STR$(P%+1)+CHR$129+NAME$(P%)+"          "
+UNIT$(P%))
11160 FORT%=0 TO 3:PRINTTAB(0,6+(T%*2));T%+1;") ";FU$(T%):NEXT
11170 PRINTTAB(5,4);"FOLLOW UP "
11180 PRINTTAB(30,6+(VAL(FUAN$(P%,1))*2));"Å<==";
:GOTOFN_OK(11190,11240)
11190 PRINTTAB(30,6+(VAL(FUAN$(P%,1))*2));"          "
11200 PRINTTAB(8,15);:AN$=FN_ANSWER("1234")
11210 IFAN$="E"THENAN$="":GOTO4630 ELSE an%=VALAN$-1
11220 PRINTTAB(30,6+(an%*2));"Å<==";:GOTOFN_OK(11160,11230)
11230 FUAN$(P%,1)=STR$(an%)
11240 PRINTTAB(0,15)"FOLLOW UP DATE :  Å";FUAN$(P%,2);
:GOTOFN_OK(11250,11260)
11250 FUAN$(P%,2)=FN_DATE(20,15,85,86)
11260 ENDPROC
11270 :
11330 :
11340 DEFPROC_ALREADY
11350 UNIT$="":ALR%=0
11360 PRINTTAB(0,6)"HAS THIS PATIENT ATTENDED BEFORE":AN$=GET$
11370 IFAN$="N" THEN ATTNO$(P%)="1":PRINTTAB(0,6)"
":ENDPROC
11380 PRINTTAB(0,8)"ATTENDANCE DATE "
11390 ATTDATE$=FN_DATE(20,8,85,86)
11400 ATT$=LEFT$(ATTDATE$,2)+MID$(ATTDATE$,4,2)+RIGHT$(ATTDATE$,2)
11410 DAT%=OPENIN":4.DTINX88"
11420 INPUT#DAT%,DATinput%,DATlength%
11430 ATT%=OPENIN":5.DC/FL88"
```

```
11440 SP%=DATinput%-DATlength%
11450 REPEAT
11460 PTR#DAT%=SP%
11470 INPUT#DAT%,DAT$
11471 date%=FN_LATER(ATT$,DAT$)
11472 IF DAT$="000000" THEN SP%=SP%-DATlength%:GOTO 11490
11473 IF date%<5 THEN SP%=SP%-DATlength%:GOTO 11490
11474 IF date%<0 THEN SP%=SP%+(DATlength%*INT(ABSdate%/2))
11475 IF date%>0 THEN SP%=SP%-(DATlength%*INT(ABSdate%/2))
11490 UNTILDAT$=ATT$
11500 INPUT#DAT%,begin%,end%:CLOSE#DAT%
11510 REPEAT
11520 PTR#ATT%=begin%:PATIENT$=""
11530 FORX%=1 TO 15:PATIENT$=PATIENT$+CHR$(BGET#ATT%):NEXT
11540 IFNAME$(P%)=PATIENT$ THEN GOTO 11565
11550  UNIT$=FN_BCK(3,1,2,"")
11560 IFUNIT$(P%)=UNIT$ THEN GOTO 11570 ELSE GOTO 11770
11565  UNIT$(P%)=FN_BCK(3,1,2,"")
11570  DOB$(P%)=FN_BCK(3,1,2,"/")
11580 ALR%=1:gg%=1
11590  PARITY$(P%)=FN_BCK(2,1,1,"+")
11600  DT$=FN_BCK(3,1,2,"/")
11610 ATTNO$(P%)=STR$(BGET#ATT%+1)
11620  LMP$(P%)=FN_BCK(3,1,2,"/")
11630  EDD$(P%)=FN_BCK(3,1,2,"/")
11640 RUBBISH=BGET#ATT%
11645 diff%=FN_LATER(TDDATE$,EDD$(P%))
:IF diff% MOD 7 =0 THEN term%=40 ELSE term%=41
11646 GEST$(P%)=STR$(term%-(diff% DIV 7))+STR$(diff% MOD 7)
11650 REFDATE$(P%)=DT$
11660 OLDDT$=FN_BCK(3,1,2,"/")
11670 REFBP$=FN_BCK(2,1,3,"/")
11680 BKBP$(P%)=FN_BCK(2,1,3,"/")
11690 BKGEST$(P%)=FN_BCK(1,1,2,"")
11700 BP28$(P%)=FN_BCK(2,1,3,"/")
11710 CON$(P%)=STR$BGET#ATT%
11720 REFERAL$(P%,1)=STR$BGET#ATT%
11730 REFERAL$(P%,1)="3"
11740 REFERAL$(P%,2)=STR$BGET#ATT%
11750 FOR Y%=0 TO 6:AVBP$=FN_BCK(2,1,3,"/"):NEXT
11760 REFBP$(P%)=AVBP$
11770 begin%=begin%+80:UNTILbegin%=end%+80
11780 CLOSE#ATT%
11790 PRINTTAB(0,6)"                                    "
11800 IFALR%=0 THENPRINTTAB(0,6)"       PATIENT NOT FOUND":PROC_SPACE
11820 PRINTTAB(0,6);"                                   "
11830 PRINTTAB(0,8);"                                   "
11840 PRINTTAB(0,9);"                                   "
11850 ENDPROC
11860 :
11870 DEFPROC_DISPLAY2
11880 PRINTBKGEST$(P%);"wk BPÇ";BKBP$(P%);"á28wk BPÇ";BP28$(P%)
11890 PRINT"From ";REF1$(VAL(REFERAL$(P%,1)));" on ";REFDATE$(P%)
11900 PRINT"Reason ";REF2$(VAL(REFERAL$(P%,2)));"ÉBP";REFBP$(P%)
11910 LATER%=FN_LATER(REFDATE$(P%),TDDATE$)
11920 PRINT"DC date ";TDDATE$;" ";LATER%;" days after referal"
11930 PRINT"CONSULTANT ";CONS$(VALCON$(P%));TAB(30);"VISIT "
```

```
;ATTNO$(P%)
11940 FORX%=0 TO 3:PRINTTAB(0);X%+1;") BP -"
;DCBP$(P%,X%);TAB(19);TEST$(X%)
;TAB(33);"-Å";RESULTS$(P%,X%):NEXT
11950 PRINT"5) BP - ";DCBP$(P%,4);TAB(19);TEST$(4);" - "
;PROT$(VAL(RESULTS$(P%,4)))
11960 IF VALRIGHT$(DCBP$(P%,6),3)<90 THEN PRINT"Av BP -É"
;DCBP$(P%,6)
;TAB(18);"áCTG - ";CTG$(VALCTGAN$(P%)) ELSE PRINT"Av BP -Å"
;DCBP$(P%,6)
;TAB(18);"áCTG - ";CTG$(VALCTGAN$(P%))
11970 PRINT"DN BP - ";DCBP$(P%,5);TAB(19);"FHR - ";FHR$(P%)
11980 PRINT"Diagnosis ";DIAG$(VAL(DIAGAN$(P%)))
11990 FU%=FN_LATER(TDDATE$,FUAN$(P%,2))
12000 PRINT"F/U-";FU$(VAL(FUAN$(P%,1)));" on ";FUAN$(P%,2)
;"(";FU%;" days later)"
12010 PROC_SPACE
12020 VDU28,0,24,39,3
12030 ENDPROC
12040 :
12042 DEFPROC_DATA
12045 ram%=0
12047 HEAD$="NEW DAYCARE (1990) ":ADD$="LOADING DATA":PROC_HEAD
12048 P%=0:axes%=0:ok%=0:gg%=0:extra%=0:first%=0
12049* K.10OLD|MGOTO30130|M
12055 PROC_DH(0,5,"ÅCOLLECTING DATA")
12060
DIMCONS$(7),REF1$(3),REF2$(5),TEST$(4),CTG$(3),FU$(3),DIAG$(4)
,UNIT$(9),LMP$(9),EDD$(9),GEST$(9),CON$(9),REFERAL$(9,2)
12070 DIMRESULTS$(9,4),CTGAN$(9),FUAN$(9,2),DIAGAN$(9),REFDATE$(9)
,REFBP$(9),DCBP$(9,6),BKBP$(9),BKGEST$(9),BP28$(9)
12080 DIMPARITY$(9),ATTNO$(9),NAME$(9),PROT$(5),DOB$(9),FHR$(9)
,ATTDATE$(9),address%(9),day$(7),mon$(12)
12090 FORD%=0 TO7:READ CONS$(D%):NEXT
12100 FORD%=0 TO3:READ REF1$(D%):NEXT
12110 FORD%=0 TO5:READ REF2$(D%):NEXT
12120 FORD%=0 TO4:READ TEST$(D%):NEXT
12130 FORD%=0 TO3:READ CTG$(D%):NEXT
12140 FORD%=0 TO3:READ FU$(D%):NEXT
12150 FORD%=0 TO4:READ DIAG$(D%):NEXT
12160 FORD%=0 TO5:READ PROT$(D%):NEXT
12170 FORD%=1 TO 12:READ mon$(D%):NEXT
12180 FORD%=0 TO 6:READ day$(D%):NEXT
12182 let$="QWERTYUIOPLKJHGFDSAZXCVBNM-' "
12183 num$="1234567890."
12190 ENDPROC
12200 :
12210 DATA BLACK,LUNAN,MACNAUGHTON,MCEWAN,WALKER,LAUGHLAND,HOWAT
,KENNEDY
12220 DATA ANTE NATAL CLINIC,GENERAL PRACTITIONER,ANTE NATAL WARD
,DAY CARE
12230 DATA ESSENTIAL HYPERTENSION,PREGNANCY HYPERTENSION,PAST HISTORY
12240 DATA PROTEINURIA,ON TREATMENT,SMALL FOR DATES
12250 DATA Urea,Urate,Haemoglobin,Platelet Count,Proteinuria
12260 DATA Not Done,REACTIVE,NONREACTIVE,ABNORMAL
12270 DATA ANTE NATAL CLINIC,ADMISSION,DAY CARE,INDUCTION
12280 DATA Normal,Mild PIH,Moderate PIH,Severe PIH
```

```
12290 DATA Essential Hypertension
12300  DATA  None,Trace,+,++,+++,++++
12310  DATA  January,February,March,April,May,June,July,August,September
,October,November,December
12320 DATA Monday,Tuesday,Wednesday,Thursday,Friday,Saturday,Sunday
12330 DATA MAIN MENU,8,TODAYS FILE,CLOSE FILE/PRINT DATA
,ACCESS MASTER FILE,LIST FROM MASTER FILE,GESTATION CALCULATOR
,CHANGE TODAYS DATE,CHANGE TIME,CHECK DELIVERED PATIENTS,12345678S
12331 DATA SPECIAL,4,ERASE CURRENT FILE,ERASE LAST DATE
,CHANGE DRIVE,ERASE PATIENT,1234E
12370 DEFPROC_INFO
12375 PROC_DH(0,5,"ÅLOADING CURRENT FILE")
12380 INFO%=OPENIN"CURRENT"
12390 LOCALP%
12400 FOR P%=0 TO 8
12405  PROC_DH(0,10,"ÉPATIENT  -  "+STR$P%)
12410  INPUT#INFO%,NAME$(P%),UNIT$(P%),LMP$(P%),EDD$(P%)
,GEST$(P%),CON$(P%),REFERAL$(P%,0),REFERAL$(P%,1)
,REFERAL$(P%,2)
12420  INPUT#INFO%,RESULTS$(P%,0),RESULTS$(P%,1),RESULTS$(P%,2)
,RESULTS$(P%,3),RESULTS$(P%,4),CTGAN$(P%),FUAN$(P%,0)
,FUAN$(P%,1)
12430  INPUT#INFO%,FUAN$(P%,2),DIAGAN$(P%),REFDATE$(P%)
,REFBP$(P%)
12440 FORX%=0 TO 6:INPUT#INFO%,DCBP$(P%,X%):NEXT
12450  INPUT#INFO%,BKBP$(P%),BKGEST$(P%),BP28$(P%),PARITY$(P%)
,ATTNO$(P%),DOB$(P%),FHR$(P%)
12460 NEXT:INPUT#INFO%,TDDATE$:CLOSE#INFO%
:D%=FN_CALCDATE(TDDATE$)
12470 PAT%=0:FOR P%=0 TO 8:IF NAME$(P%)<>"              "THEN
PAT%=PAT%+1
12480 NEXT
12485 IFR%<>1THENPROC_TIME
12490 ENDPROC
12500  :
12510  DEFFN_BCK(byte%,times%,l%,slash$)
12520  tot$=""
12530 FOR x%=1 TO byte%
12540 IFtimes%=1 THEN t$=STR$(BGET#ATT%)
ELSE  t$=STR$(VAL(CHR$(BGET#ATT%))*times%)
12550 IF LENt$<l% THEN t$="0"+t$:GOTO 12550
12560  tot$=tot$+t$
12570 IF x%<byte% THEN tot$=tot$+slash$
12580 NEXT
12590  =tot$
12600  :
12690 DEFPROC_SAVECURRENT
12695 IF TDDATE$="00/00/00" AND ok%=0 THEN ENDPROC
12697 CLS:PROC_DH(5,5,"ÇSAVING CURRENT DATA")
12700 INFO%=OPENUP"CURRENT"
12710 LOCAL P%
12720 FOR P%=0 TO 8
12725  PROC_DH(5,8,"ÉPATIENT  "+STR$(P%+1))
12730  PRINT#INFO%,NAME$(P%),UNIT$(P%),LMP$(P%),EDD$(P%)
,GEST$(P%),CON$(P%),REFERAL$(P%,0),REFERAL$(P%,1),REFERAL$(P%,2)
,RESULTS$(P%,0),RESULTS$(P%,1),RESULTS$(P%,2),RESULTS$(P%,3)
,RESULTS$(P%,4),CTGAN$(P%),FUAN$(P%,0,FUAN$(P%,1)
```

```
12740PRINT#INFO%,FUAN$(P%,2),DIAGAN$(P%),REFDATE$(P%)
,REFBP$(P%)
12760 FORX%=0 TO 6:PRINT#INFO%,DCBP$(P%,X%):NEXT
12770  PRINT#INFO%,BKBP$(P%),BKGEST$(P%),BP28$(P%),PARITY$(P%)
,ATTNO$(P%),DOB$(P%),FHR$(P%)
12780 NEXT
12790 PRINT#INFO%,TDDATE$
12800 CLOSE#INFO%
12810 ENDPROC
12820 :
13000 DEFPROC_ERASEPATIENT
13001  first%=0
13010 ADD$="ERASE PATIENT":HEAD$="DAYCARE":PROC_HEAD
13020 FORP%=0 TO PAT%-1
13030  PROC_DH(0,P%*2,STR$(P%+1)+CHR$133+NAME$(P%)+"  "
+UNIT$(P%))
13040 NEXT
13050 PROC_DH(0,P%*2,CHR$133+"INPUT PATIENT TO ERASE")
:A$=FN_ANSWER("123456789")
13060 IF A$="E" THEN PROC_SAVECURRENT:ENDPROC
13065 CLS
13070 PROC_DH(0,5," ERASING PATIENT "+A$)
13075  A$=STR$(VALA$-1)
13080 INFO%=OPENIN"CURRENT"
13090 LOCALP%
13100 FOR P%=0 TO 8
13104 IF P%=VALA$ AND first%=1 THEN P%=VALA$+1
13105 IF P%=8 THEN PROC_BLANK(8):GOTO13170
13110 PROC_DH(0,10," READING PATIENT - "+STR$P%)
13120  INPUT#INFO%,NAME$(P%),UNIT$(P%),LMP$(P%),EDD$(P%)
,GEST$(P%),CON$(P%),REFERAL$(P%,0),REFERAL$(P%,1),REFERAL$(P%,2)
13130  INPUT#INFO%,RESULTS$(P%,0),RESULTS$(P%,1),RESULTS$(P%,2)
,RESULTS$(P%,3),RESULTS$(P%,4),CTGAN$(P%),FUAN$(P%,0)
,FUAN$(P%,1)
13140  INPUT#INFO%,FUAN$(P%,2),DIAGAN$(P%),REFDATE$(P%)
,REFBP$(P%)
13150 FORX%=0 TO 6:INPUT#INFO%,DCBP$(P%,X%):NEXT
13160  INPUT#INFO%,BKBP$(P%),BKGEST$(P%),BP28$(P%),PARITY$(P%)
,ATTNO$(P%),DOB$(P%),FHR$(P%)
13165 IF first%=0 AND P%=VALA$ THEN first%=1:P%=P%-1
13170 NEXT
13175 INPUT#INFO%,TDDATE$:CLOSE#INFO%:D%=FN_CALCDATE(TDDATE$)
13180 PAT%=0:FOR P%=0 TO 8:IF NAME$(P%)<>"            "THEN
PAT%=PAT%+1
13192  PRINTP%
13200 NEXT
13205 CLS
13210 GOTO13020
13220 NEXT
13300 DEFPROC_BLANK
20000 DEFPROC_TIME
20010 CLS:ADD$="TIME CHECK":PROC_HEAD
20020  MIN$=STR$((TIME DIV 6000)MOD 60)
:HR$=STR$((TIME DIV 360000)MOD 24)
20030  IFLENHR$<2THENHR$="0"+HR$
20040  IFLENMIN$<2THENMIN$="0"+MIN$
20050  PROC_DH(0,5,"ÂTHE TIME IS "+HR$+":"+MIN$+" OK?")
```

```
:AN$=INKEY$(6000)
20060 IF AN$="Y"THEN R%=1:ENDPROC
20070 IFAN$<>"N" THEN 20020
20080 CLS:PROC_DH(8,5,"ÅINPUT TIME")
20090  PRINTTAB(0,9);"HOURS  (00)"
20100  HOUR$=FN_INPUT(20,9,2,num$)
20110  PRINTTAB(0,11);"MINUTES  (00)"
20120  MIN$=FN_INPUT(20,11,2,num$)
20130  TIME=((VALHOUR$*60+VALMIN$)*60)*100
20140 GOTO20020
20150 ENDPROC
20160  :
20170 DEFFN_NAMEINPUT(X%,Y%)
20180  NAME$=FN_INPUT(X%,Y%,15,let$)
20190 IFMID$(NAME$,2,1)<>" " OR MID$(NAME$,3,1)=" " THEN NAME$=""
20200  NAME$=NAME$+STRING$(15-LEN(NAME$)," ")
:GOTOFN_OK(20180,20210)
20210 =NAME$
20220  :
20230 DEFFN_CALCEDD(d$,w%,y%)
20240 LOCALd%,e%,y%
20245  y%=VALRIGHT$(d$,2)
20250 d%=FN_CALCDATE(d$)
20260  e%=d%-w%+280
20270 IF e%>365 THEN y%=y%+1:e%=e%-365
20280 =FN_CALCDAY(e%,STR$y%)
20290  :
20300 DEFFN_OK(g%,n%)
20301 IF gg%=1 THEN =n%
20305 LOCALk$:PRINT;CHR$136;" Y/N";:k$=FN_YN:VDU127,127,127
:IFk$="N"THEN=g% ELSE =n%
20310  :
20320 DEFFN_DATE(X%,Y%,low%,high%)
20325  high%=90
20330 LOCAL D$,add$,key%,valid$
20340  D$="":valid$="1234567890"
20350  PRINTTAB(X%,Y%);"../../..";STRING$(9,CHR$(8));"  ";:*FX15,1
20360 key%=GET:IFkey%=13 AND D$="" THEN =D$
20370 IFkey%=47 THEN GOTO20360
20380 IFkey%=13 AND LEND$=8 THEN GOTO20440
20390 IFkey%=127 AND (LEND$ MOD 3<>0) THEN D$=LEFT$(D$,LEN(D$)-1)
:PRINTCHR$(key%);".";CHR$(8);:GOTO20360
20400 IFkey%=127 AND (LEND$ MOD 3=0) THEN D$=LEFT$(D$,LEN(D$)-2)
:PRINTCHR$(key%);CHR$(key%);"./";CHR$(8);CHR$(8);:GOTO20360
20410 IFLEN(D$)=8 ORINSTR(valid$,CHR$(key%))=0 VDU7:GOTO20360
20420  PRINTCHR$(key%);:D$=D$+CHR$(key%)
:IFLEND$=2 OR LEND$=5 THEN D$=D$+"/":PRINT"/";
20430 GOTO20360
20440 IF VAL(MID$(D$,4,2))>12 THENVDU7:GOTO20350
20450 I%=VAL(RIGHT$(D$,2)) MOD 4:IFI%<>0 THEN add$="303232332323"
ELSE  add$="313232332323"
20460  IFVAL(LEFT$(D$,2))>28+VAL(MID$(add$,VAL(MID$(D$,4,2)),1))
THENVDU7:GOTO20350
20470 IFVAL(RIGHT$(D$,2))>high% OR  VAL(RIGHT$(D$,2))<low%
THENVDU7:GOTO20350
20480  GOTOFN_OK(20350,20490)
20490  =D$
```

```
20500 :
20510 DEFFN_CALCDATE(d$)
20520 LOCALd%,add$,alt%,l%
20530  add$="000031059090120151181212243273304334"
20540 IFLENd$=8THEN alt%=0 ELSE alt%=-1
20550  d%=VAL(LEFT$(d$,2))+VALMID$(add$,VALMID$(d$,4+alt%,2)*3-2,3)
20560 IFVALRIGHT$(d$,2)MOD 4=0 AND VALMID$(d$,4+alt%,2)>2
THENd%=d%+1
20570 =d%
20580 :
20590 DEFFN_CALCDAY(d%,YR$)
20600 LOCALd$,add$,mon%,day%,m$,l%
20610 l%=VAL(RIGHT$(YR$,2)) MOD 4
20620  IFl%<>0 THEN add$="000031059090120151181212243273304334"
ELSE  add$="000031060091121152182213244274305335"
20630 mon%=-1:REPEAT:mon%=mon%+1:UNTIL
d%<VALMID$(add$,mon%*3+1,3) OR mon%=12
20640  day%=d%-VALMID$(add$,(mon%-1)*3+1,3):d$=STR$day%:IFLENd$=1
THEN d$="0"+d$
20650 m$=STR$mon%:IF LENm$=1 THEN m$="0"+m$
20660  =d$+"/"+m$+"/"+YR$
20670 :
20680 DEFFN_DAYNAME(date$)
20682 LOCAL y%,m%,d%,c%,a%,d$
20684 RESTORE20700
20686  y%=VAL(RIGHT$(date$,2)):d%=VAL(LEFT$(date$,2))
20688  m%=VAL(MID$(date$,4,2))-2:IF m%<1 THEN m%=m%+12:y%=y%-1
20690  c%=(1900+y%) DIV 100
20692 a%=(260*m%-19) DIV 100 + y% DIV 4  + c% DIV 4 +d%+y%-c%*2
20694  FOR D%=1 TO (INT((a%/7-INT(a%/7))*7+0.1))
20696 READ d$
20698 NEXT
20700 DATAMon,Tues,Wednes,Thurs,Fri,Satur,Sun
20702  =d$+"day"
20704 :
20706 DEFFN_MONTHNAME(date$)
20708 LOCAL M%,m$:RESTORE 20714
20710 FOR M%=1 TO VAL(MID$(date$,4,2)):READ m$:NEXT
20712  =m$
20714  DATA January,February,March,April,May,June,July,August,September
,October,November,December
20716 :
20718 DEFFN_DAYNUMBER(date$)
20720 LOCAL d%,d$
20722  d%=VAL(LEFT$(date$,2))
20724 IF d%>3 AND d%<21 THEN=STR$d%+"th"
20726 d%=d% MOD 10
20728 IF d%=1 THEN =STR$d%+"st"
20730 IF d%=2 THEN =STR$d%+"nd"
20732 IF d%=3 THEN =STR$d%+"rd" ELSE =STR$d%+"th"
20734 :
20736 DEFFN_NAMEDAY(d%,YR$)
20738 LOCALd$,m$
20740 date$=FN_CALCDAY(d%,YR$)
20742 =FN_DAYNAME(date$)+" the "+FN_DAYNUMBER(date$)+" of "
+FN_MONTHNAME(date$)+", 19"+YR$
20746 :
```

```
20760 :
20770 DEFFN_LATER(f$,s$)
20780 LOCAL f%,s%
20790 f%=FN_CALCDATE(f$)+(VALRIGHT$(f$,2)*365)
:s%=FN_CALCDATE(s$)+(VALRIGHT$(s$,2)*365)
20800 IF RIGHT$(f$,2)="84" AND f%>30719 THEN YR%=1 ELSE YR%=0
20810 =s%-f%+YR%
20812 :
20814 DEFPROC_GESTLMP
20816 CLS
20818 PRINTTAB(5,5)"LMP ":lmp$=FN_DATE(20,5,85,87)
20820 IF TDDATE$="00/00/00" THEN PRINTTAB(5,7)"TODAYS DATE "
:TDDATE$=FN_DATE(20,7,86,87)
20824 PRINTTAB(5,10)"ÅGestation isÇ ";FN_GEST(lmp$,TDDATE$)
20825 PRINT'"Ç<R>eturn to menu É<A>gain":A$=GET$:IF A$="A" THEN GOTO 20816
20826 ENDPROC
20828 :
20830 DEFFN_GEST(f$,s$):LATER%=FN_LATER(f$,s$)
:=STR$(LATER% DIV 7)+"+"+STR$(LATER% MOD 7)
20840 :
20850 DEFFN_AGE(f$,s$):LATER%=FN_LATER(f$,s$):=LATER% DIV 365
20855 :
20860 DEFPROC_HEAD:VDU26:CLS:X%=(34-(LEN(HEAD$)+LEN(ADD$)))/2
20870 PROC_DH(X%,0,CHR$132+HEAD$+" - "+ADD$)
20880 PRINTTAB(X%+1,2);CHR$147+STRING$(LEN(HEAD$)
+LEN(ADD$)+3,"|")
20890 VDU28,0,24,39,3:ENDPROC
20900 :
20910 DEFFN_YN:LOCALkey$:*FX15,1
20920 REPEAT:key$=CHR$(GET AND &DF):UNTIL INSTR("YN",key$):=key$
20930 :
20940 DEFPROC_SPACE:*FX15,1
20950 PRINT"TAB(7);CHR$132+"Press"+CHR$131+"SPACE"
+CHR$132+"to continue":REPEAT:UNTIL GET=32:ENDPROC
20960 :
20970 DEFPROC_DH(X%,Y%,A$):PRINTTAB(X%,Y%);CHR$141;A$
:PRINTTAB(X%);CHR$141;A$:ENDPROC
20980 :
20990 DEFFN_INPUT(X%,Y%,len%,valid$)
21000 LOCALinput$,key%
21010 input$=""
21020 PRINTTAB(X%,Y%);STRING$(len%,".");STRING$(len%+1,CHR$(8));" ";
:*FX15,1
21030 key%=GET:IFkey%=13 THEN =input$
21040 IFkey%=127 AND input$=""THEN =input$
21050 IFkey%=127 THEN input$=LEFT$(input$,LEN(input$)-1)
:PRINTCHR$(key%);".";CHR$(8);:GOTO21030
21060 IFLEN(input$)=len% ORINSTR(valid$,CHR$(key%))=0 VDU7:GOTO21030
21070 PRINTCHR$(key%);:input$=input$+CHR$(key%):GOTO21030
21080 :
21090 DEFFN_BP(X%,Y%)
21100 LOCAL D$,key%,valid$
21110 D$="":valid$="1234567890"
21120 PRINTTAB(X%,Y%);".../...";STRING$(8,CHR$(8));" ";:*FX15,1
21130 key%=GET:IFkey%=13 AND D$="" THEN =D$
21135 IFkey%=13 AND D$="000/000" THEN =D$
21140 IFkey%=47 THEN GOTO21130
```

```
21150 IFkey%=13 AND LEND$=7 THEN GOTO21220
21160 IFkey%=13 AND LEND$=6 THEN D$=LEFT$(D$,4)+"0"+RIGHT$(D$,2)
:PRINTTAB(X%,Y%)D$;:GOTO21220
21170 IFkey%=127 AND LEND$<>4 THEN D$=LEFT$(D$,LEN(D$)-1)
:PRINTCHR$(key%);".";CHR$(8);:GOTO21130
21180 IFkey%=127 AND LEND$=4 THEN D$=LEFT$(D$,LEN(D$)-2)
:PRINTCHR$(key%);CHR$(key%);"./";CHR$(8);CHR$(8);:GOTO21130
21190 IFLEN(D$)=7 ORINSTR(valid$,CHR$(key%))=0 VDU7:GOTO21130
21200 PRINTCHR$(key%);:D$=D$+CHR$(key%):IFLEND$=3 THEN
D$=D$+"/":PRINT"/";
21210 GOTO21130
21220 IF VAL(RIGHT$(D$,3))>=VAL(LEFT$(D$,3))THENVDU7:GOTO21120
21230 IF VALRIGHT$(D$,3)>250 OR VALLEFT$(D$,3)>250
THENVDU7:GOTO21120
21240 IFVALRIGHT$(D$,3)=0 OR VALLEFT$(D$,3)=0 THENVDU7:GOTO21120
21250 GOTOFN_OK(21130,21260)
21260 =D$
21270 :
21280 DEFFN_ANSWER(A$):LOCAL key$:*FX15,1
21282* FX15,1
21285 VDU28,0,24,39,3
21290 A$=A$+"E"
21300 REPEAT
21310 MIN$=STR$((TIME DIV 6000)MOD 60):HR$=STR$((TIME DIV
360000)MOD 24)
:SEC$=STR$((TIME DIV 100)MOD 60):SEC$=LEFT$(SEC$,2)
21320 IFLENSEC$ <2THENSEC$="0"+SEC$
21330 IFLENHR$<2THENHR$="0"+HR$
21340 IFLENMIN$<2THENMIN$="0"+MIN$
21350
PROC_DH(0,19,CHR$131+CHR$136+"INPUT"+CHR$137+"ANSWER"+CHR$132
+"E TO EXIT"+"Å"+HR$+":"+MIN$+":"+SEC$)
21360 key$=INKEY$(100):IFkey$="e"THENkey$="E"
21370 IFLENkey$=0 THEN 21310
21380 UNTIL INSTR(A$,key$)
21390 =key$
21400 :
22000 DEFPROC_GESTATION
22010 CLS:PRINTTAB(8,2)"ÖGESTATION CALCULATOR"
22020 PRINTTAB(5,5)"Å<L>MPÇ<S>CANÉ<E>DDÑ<M>ENU"
22025 A$=GET$
22030 IF A$="L" THEN PROC_GESTLMP
22035 IF A$="M" THEN ENDPROC
22040 IF A$="E" THEN PROC_GESTEDD
22050 IF A$="S" THEN PROC_GESTSCAN
22060 GOTO 22010
22100 DEFPROC_GESTEDD
22110 CLS
22120 PRINTTAB(5,5)"EDD ":edd$=FN_DATE(20,5,85,87)
22130 IF TDDATE$="00/00/00" THEN PRINTTAB(5,7)"TODAYS DATE "
:TDDATE$=FN_DATE(20,7,86,87)
22140 LATER%=FN_LATER(TDDATE$,edd$)
22145 IF LATER% MOD 7=0 THEN PRINTTAB(5,10)"ÅGestation isÇ "
;(40-(LATER% DIV 7));" + 0"
22150 IF LATER% MOD 7<>0 THEN PRINTTAB(5,10)"ÅGestation isÇ "
;(40-(LATER% DIV 7+1));" + ";(7-LATER% MOD 7)
22160 PRINT'"Å<A>gain Ç<R>eturn to menu"
```

```
22170 A$=GET$:IF A$="A" THEN GOTO 22110
22180 ENDPROC
22190 DEFPROC_GESTSCAN
22200 CLS
22210 PRINTTAB(5,5)"SCAN DATE ":scan$=FN_DATE(20,5,85,87)
22215 PRINTTAB(5,7)"SCAN GEST 00+0"
:gest$=FN_INPUT(20,7,4,"1234567890+"):IF LENgest$<>4 THEN
VDU7:GOTO22215
22220 IF TDDATE$="00/00/00" THEN PRINTTAB(5,9)"TODAYS DATE "
:TDDATE$=FN_DATE(20,9,86,87)
22230 LATER%=FN_LATER(scan$,TDDATE$)
22240 wk%=VALgest$:day%=VALRIGHT$(gest$,1)
22250 day%=day%+wk%*7
22260 PRINTTAB(5,10)"ÅGestation isÇ ";(LATER%+day%) DIV 7;" +
";(LATER%+day%) MOD 7
22270 PRINT'"Å<A>gain Ç<R>eturn to menu"
22280 A$=GET$:IF A$="A" THEN GOTO 22200
22290 ENDPROC
30000 REM ERROR TRAP
30001 REPORT:PRINTERL
30004 IF ERL>=4500 AND ERL<=4550 THEN
DINAinput%=DINAinput%+50:PROC_BACK:GOTO4170
30005 VDU26:MODE 7
30010* FX2,0
30015 CLOSE#0:IF axes%<>1 THEN PROC_SAVECURRENT
30020 CLS:IF ERR=17 THENPROC_DH(0,10,CHR$131
+"YOU HAVE PRESSED THE"+CHR$132+"ESCAPE"+CHR$131+"KEY"):GOTO30080
30060 :
30065 IF ERL>4000 AND ERL <5600 THEN GOTO30070 ELSE CLS
30070 IF ERR<>17 THEN
PROC_DH(0,5,CHR$131+"THE"+CHR$132+"ERROR"):REPORT
:PROC_DH(0,10,CHR$131+"HAS BEEN MADE IN LINE "+STR$ERL)
30080 PROC_DH(1,13,"ÅDO YOU WISH TO
CONTINUE"+CHR$135+"==>"+CHR$130+"(Y)")
30090 PROC_DH(1,15,"ÅDO YOU WISH TO ESCAPE "
+CHR$135+"==>"+CHR$130+"(N)")
30100 Y$=FN_YN
30110 IFY$="Y" AND axes%=0 THEN GOTO 110
30120 IFY$="Y" AND axes%<>0 THEN RUN ELSE END
30130 CLS:PROC_DH(1,7,"ÅYOU HAVE PRESSED THE"
+CHR$132+"BREAK"+CHR$129+"KEY")
30140 PROC_DH(0,10,CHR$131+"ALL DATA NOT SAVED HAS BEEN LOST")
30150 PROC_DH(1,13,"ÅDO YOU WISH TO
CONTINUE"+CHR$135+"==>"+CHR$130+"(Y)")
30160 PROC_DH(1,15,"ÅDO YOU WISH TO ESCAPE "
+CHR$135+"==>"+CHR$130+"(N)")
30170 Y$=FN_YN
30180 IFY$="Y"THEN RUN ELSE END
```

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